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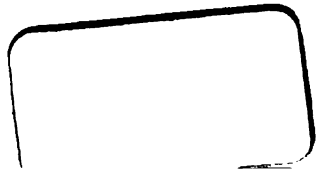

TRANSACTIONS

OF THE

ASSOCIATION OF AMERICAN PHYSICIANS.

NINETEENTH SESSION,

HELD AT WASHINGTON, D. C.,

MAY 10 AND 11, 1904.

VOLUME XIX.

PHILADELPHIA:
PRINTED FOR THE ASSOCIATION.
1904.

NOTICE.

THE Association assumes no responsibility for the statements and opinions expressed in the papers read at its meetings

DORNAN, PRINTER,
701-709 ARCH STREET,
PHILADELPHIA.

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ASSOCIATION OF AMERICAN PHYSICIANS

OFFICERS FOR THE YEAR 1904-1905.

PRESIDENT.
EDWARD L. TRUDEAU, M.D.

VICE-PRESIDENT.
FRANK BILLINGS, M.D.

SECRETARY.
HENRY HUN, M.D.

RECORDER.
SOLOMON SOLIS COHEN, M.D.

TREASURER.
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V. C. VAUGHAN, M.D.
GEORGE M. KOBER, M.D.
F. FORCHHEIMER, M.D.

REPRESENTATIVE ON THE EXECUTIVE COMMITTEE OF THE CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS.
WILLIAM OSLER, M.D.

ALTERNATE REPRESENTATIVE.
FRANCIS H. WILLIAMS, M.D.

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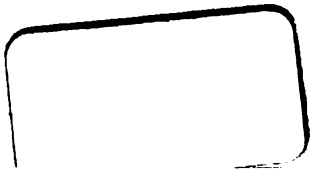


ELECTED

1896. STEWART, D. D., 1633 Spruce St., Philadelphia.
*1886. STEWART, JAMES, 285 Mountain St., Montreal, Canada.
1889. STOCKTON, CHARLES G., 436 Franklin St., Buffalo, N. Y.
1904. STRONG, RICHARD P., Manila, the Philippines.
1899. THACHER, J. S., 33 West 39th St., New York.
1897. THAYER, W. S., 406 Cathedral St., Baltimore.
1899. THOMPSON, W. GILMAN, 34 East 31st St., New York.
1889. THOMSON, WM. H., 23 East 47th St., New York.
*1886. TRUDEAU, EDWARD L., Saranac Lake, Franklin Co., N. Y.
*1886. TYSON, JAMES, 1506 Spruce St., Philadelphia.
1889. VAUGHAN, VICTOR C., University of Michigan, Ann Arbor, Mich.
1898. VICKERY, HERMAN F., 263 Beacon St., Boston.
*1886. WARD, SAMUEL B., 281 State St., Albany, N. Y.
1901. WARTHIN, ALDRED S., University of Michigan, Ann Arbor, Mich.
*1886. WELCH, WM. H., 935 St. Paul St., Baltimore.
1898. WESBROOK, F. F., State Board of Health, Minneapolis, Minn.
*1886. WILKINS, GEORGE, 899 Dorchester St., Montreal, Canada.
1894. WILLIAMS, FRANCIS H., 505 Beacon St., Boston.
1901. WILLIAMS, HERBERT U., University of Buffalo, Buffalo, N. Y.
*1886. WILSON, JAMES C., 1509 Walnut St., Philadelphia.
1898. WITHINGTON, CHARLES F., 35 Bay State Road, Boston.
*1886. WOOD, HORATIO C., 1925 Chestnut St., Philadelphia.
1899. WRIGHT, J. H., Pathological Laboratory, Massachusetts General Hospital, Boston.

HONORARY MEMBERS.

Elected Active Member.	Elected Honorary Member.	
1886.	1902.	BALL, A. BRAYTON, M.D., 42 West 36th St., New York.
1886.	1887.	BILLINGS, JOHN S., M.D., Astor Library, Lafayette Place, New York.
1886.	1897.	CHEW, SAMUEL C., M.D., 215 West Lanvale St., Baltimore.
1890.	1902.	FISK, S. A., M.D., Denver Club, Denver, Col.
1886.	1901.	FOLSOM, CHARLES F., M.D., 15 Marlborough St., Boston.
1886.	1900.	GUITÉRAS, JOHN, M.D., Havana, Cuba.
1886.	1902.	HAYS, I. MINIS, M.D., 268 S. 21st St., Philadelphia.
1890.	1902.	HURD, H. M., M.D., Johns Hopkins Hospital, Baltimore.
1886.	1902.	LYMAN, H. M., M.D., 220 Ashland Boulevard, Chicago.
1889.	1904.	LOVING, STARLING, M.D., 229 East State St., Columbus, Ohio.
1891.	1900.	MASON A. LAWRENCE, M.D., 265 Clarendon St., Boston.
1886.	1897.	MILES, F. T., M.D., 514 Cathedral St., Baltimore.
1886.	1898.	POLK, WM. M., M.D., 7 East 36th St., New York.
1886.	1904.	ROBINSON, BEVERLEY, M.D., 37 West 35th St., New York.
1887.	1902.	STARR, LOUIS, M.D., 1818 S. Rittenhouse Square, Philadelphia.
1889.	1904.	WALCOTT, HENRY P., M.D., 11 Waterhouse St., Cambridge, Mass.

DECEASED MEMBERS.

* Honorary Members.

Date of Election.	
*1890.	BARKER, FORDYCE, M.D., New York.
*1886.	BOWDITCH, HENRY I., M.D., Boston.
1886.	BRUEN, EDWARD T., M.D., Philadelphia.
1886.	BUSEY, SAMUEL C., M.D., Washington, D. C.
*1886.	CLARK, ALONZO, M.D., New York.
*1886.	CLYMER, MEREDITH, M.D., New York.
1886.	DA COSTA, J. M., M.D., Philadelphia.
1889.	DABNEY, WILLIAM C., M.D., University of Virginia.
*1886.	DALTON, JOHN C., M.D., New York.
*1886.	DANA, ISRAEL T., M.D., Portland, Maine.
1886.	DONALDSON, FRANK, M.D., Baltimore.
1886.	DRAPER, WILLIAM H., M.D., New York.
1886.	FORMAD, HENRY F., M.D., Philadelphia.
1889.	GEDDINGS, W. H., M.D., Aiken, S. C.
1886.	GRAHAM, J. E., M.D., Toronto, Canada.
1886.	HOWARD, R. PALMER, M.D., Montreal, Canada.
1886.	HUDSON, E. DARWIN, JR., M.D., New York.
1886.	HUTCHINSON, JAMES H., M.D., Philadelphia.
1886.	JOHNSON, HOSMER A., M.D., Chicago.
1899.	JOHNSTON, W. G., M.D., Montreal, Canada.
1886.	JOHNSTON, W. W., M.D., Washington, D. C.
*1886.	LEIDY, JOSEPH, M.D., Philadelphia.
1886.	LOOMIS, ALFRED L., M.D., New York.
1886.	MCBRIDE, THOMAS A., M.D., New York.
1890.	MACDONNELL, R. P., M.D., Montreal, Canada.
*1886.	METCALF, JOHN T., M.D., Cold Spring, N. Y.
1886.	MINOT, FRANCIS, M.D., Boston.
1898.	PACKARD, FREDERICK A., M.D., Philadelphia.
1886.	PEPPER, WILLIAM, M.D., Philadelphia.
1888.	PRENTISS, D. W., M.D., Washington, D. C.
1896.	REED, WALTER, M.D., Washington, D. C.
1887.	REEVES, JAMES E., M.D., Chattanooga, Tenn.
*1886.	ROCHESTER, THOMAS F., M.D., Buffalo. N. Y.
1889.	ROOSEVELT, J. WEST, M.D., New York.
1886.	ROSS, GEORGE, M.D., Montreal, Canada.
1886.	SCHMIDT, H. D., M.D., New Orleans.
*1886.	STILLÉ, ALFRED, M.D., Philadelphia.
1886.	THACHER, JAMES K., M.D., New Haven, Conn.
1886.	WHITTAKER, JAMES T., M.D., Cincinnati.

ASSOCIATION

OF

AMERICAN PHYSICIANS.

CONSTITUTION.

As Amended May 10, 1904.

Article I.

Object and Name.

This Association has for its object the advancement of scientific and practical medicine, and shall be known as The Association of American Physicians.

Article II.

Members.

The number of active members shall be limited to one hundred and thirty-five. Physicians of sufficient eminence to merit the distinction may, to a number not exceeding twenty-five, be elected honorary members, and as such shall be entitled to attend all meetings and to take part in the proceedings, but not to vote.

Membership shall lapse by reason of absence from three successive annual meetings without reason given acceptable to the Council. An excused absence shall not be regarded as an attendance. Membership may be forfeited for reasons deemed sufficient by the Association.

Article III.

Officers.

The Officers of the Association shall be a President, a Vice-President, a Secretary, a Recorder, a Treasurer—all to be elected annually;

five Councillors—one to be elected each year for a term of five years; and a Representative to serve on the Executive Committee of the Congress of American Physicians and Surgeons, to be elcted at the annual meeting immediately following the Congress.

Article IV.

Duty of Officers.

The duties of the President, Vice-President, Secretary and Treasurer shall be those usually assigned to these officers.

The Recorder shall secure the papers read and also proper notes of the discussions thereon, and shall publish the annual volume of Transactions.

The five Councillors shall constitute a Committee of Nomination of Officers, and as such shall present a report at the commencement of the morning session of the last day of the annual meeting, at the conclusion of which session the election shall be held by ballot.

The Representative on the Executive Committee of the Congress shall have full power to represent the Association on all ordinary questions, but must be authorized by the Council of this Association before assenting to the admission of any Society to the Congress.

Article V.

Council.

The officers of the Association shall constitute the Council, of which four members shall constitute a quorum. It shall be the duty of the Council to supervise the affairs of the Association, to make all the arrangements for the annual meeting, to suggest the subject for debate, and to consider the nominations for membership and report on them at the meeting at which they shall be balloted on.

Article VI.

Meetings.

1. The Association shall hold an annual meeting in the City of Washington, D. C., at a time designated by the Council.

2. The President shall call the meeting to order and open the session by an address not exceeding half an hour in length. In his absence the Vice-President shall preside, and in the absence of both these officers, the senior Councillor.

3. Then shall follow original communications, discussions on subjects of general interest in the department of medicine and pathology, demonstrations in pathology and miscellaneous business.

4. Authors of papers and referees and co-referees who open a discussion shall not occupy more than thirty minutes each; and in the discussion following, the remarks of each speaker shall be limited to ten minutes.

5. The referees, co-referees and authors of papers shall send abstracts of their papers to the Council for distribution to members previous to the meeting.

Article VII.

Quorum.

Any number of members present at the appointed time of the annual meeting shall constitute a quorum for the transaction of ordinary business, but for the election of members, fifteen shall be necessary for a quorum, and for altering the Constitution, twenty-five members shall be necessary.

Article VIII.

Election of Members.

Nominations to membership, signed by two members who are not officers of the Association, must be made in writing at an annual meeting of the Association; and within six months of the time of nomination the nominators shall transmit to the Council letters stating the qualifications of the nominee, and also a list of his professional positions and publications. The Council shall report the name of each nominee to the members of the Association by letter prior to acting upon the same. The Council shall report those nominations which are approved by it to the next annual meeting for action. The election of new members shall take place on the second day of the meeting. An affirmative vote of three-fourths of the members present shall be necessary for the election of active members, but for the election of honorary members a unanimous vote of those present shall be required.

Article IX.

Annual Dues.

The annual dues of the Association shall be such sum as the Council from time to time may fix, from the payment of which honorary members shall be exempt.

Article X.

Amendments to the Constitution.

Amendments to the Constitution must be proposed in writing by five members at an annual meeting, and must be acted upon at the succeeding annual meeting, the notices for which shall contain an announcement of the proposed amendments; and such amendments shall require for their adoption an affirmative vote of three-fourths of those present

MINUTES

OF THE

NINETEENTH ANNUAL MEETING.

Held at Washington, D. C., May 10 *and* 11, 1904.

The following members were present during the meeting:

A. C. Abbott,
I. Adler,
G. Baumgarten,
F. Billings,
B. M. Bolton,
C. S. Bond,
R. C. Cabot,
C. Cary,
S. S. Cohen,
W. T. Councilman,
G. Dock,
A. R. Edwards,
J. Ewing,
W. E. Fischel,
M. H. Fussell,
T. B. Futcher,
J. P. C. Griffith,
H. A. Hare,
H. Hun,
A. Jacobi,
E. G. Janeway,
E. P. Joslin,
F. P. Kinnicutt,
J. J. Kinyoun,
G. M. Kober,
H. Koplik,
M. J. Lewis,
M. Longstreth,
S. Loving,
W. G. MacCallum,
F. B. Mallory,
S. J. Meltzer,
S. W. Mitchell,
J. H. Musser,
W. P. Northrup,
F. G. Novy,
E. L. Opie,
W. Osler,
W. H. Park,
G. L. Peabody,
M. Prince,
J. J. Putnam,
B. Sachs,
W. Sinkler,
B. W. Sippy,
A. Stengel,
G. M. Sternberg,
C. G. Stockton,
J. S. Thacher,
W. S. Thayer,
W. G. Thompson,
W. H. Thomson,
J. Tyson,
S. B. Ward,
W. H. Welch,
J. C. Wilson,
C. F. Withington,
H. C. Wood.

TUESDAY, MAY 10TH.—MORNING SESSION.

The Association was called to order at 10 A.M. by President Councilman, who read the President's Address.

The Secretary read the recommendation from the Council that the membership of the Association be increased from one hundred and twenty-five to one hundred and thirty-five.

It was resolved that the Constitution be so amended that the first sentence of Article II. shall read: "The number of active members shall be limited to one hundred and thirty-five."

The Secretary read the list of those nominees recommended by the Council for election to active membership in the Association.

On motion of Dr. Janeway, the President appointed a committee, consisting of Drs. Janeway, Welch and Billings, to co-operate with the Board of Trustees to raise funds for a memorial to the late Major Walter Reed, M.D.

The Treasurer's report was accepted and referred to an Auditing Committee consisting of Drs. Peabody and Hare.

Dr. Meltzer read a paper entitled "The Influence of Suprarenal Extract upon Absorption and Elimination, with Demonstration," which was discussed by Drs. Thompson, Hare, and Meltzer.

Dr. Fussell read a paper entitled "Polyuria in Typhoid Fever," which was discussed by Drs. Dock, Thompson, Cabot, Osler, Withington, Thayer and Fussell.

Dr. Thayer read a paper entitled "Cases of Venous Thrombosis Occurring in the Course of Typhoid Fever," which was discussed by Drs. Peabody, Stengel, Welch, Prince, Cary, Thompson, Tyson, Osler and Thayer.

Dr. Stengel read a paper entitled "Clinical Studies in Arteriosclerosis," which was discussed by Drs. Kinnicutt, Cohen and Stengel.

Dr. Cabot read a paper entitled "An Investigation of the Effects of Cardiac Stimulants, Especially Strychnin, on the Blood Pressure in Febrile Conditions," which was discussed by Drs. Stengel, Hare and Cabot.

Dr. W. H. Thomson read a paper entitled "A Supposed Cause of High-tension Pulse in Nephritis," which was discussed by Drs. Peabody and Thomson.

Dr. W. G. Thompson read a paper entitled "Poisoning by Illuminating Gas: a Clinical Study of Fifty Cases," which was discussed by Drs. Weir Mitchell, Stengel, Peabody, Kinnicutt, Hare, Cohen and Thompson.

The Auditing Committee reported that they had examined the Treasurer's books and vouchers and found them to be correct. This report was accepted and the committee was discharged.

Dr. Weir Mitchell read a letter from Dr. Noguchi, who, as a "Science

Assistant in the Carnegie Institute," is working in the Copenhagen Serum Institute, detailing certain experimental work in regard to crotalia venom.

Adjourned at 1.05 P.M.

AFTERNOON SESSION.

The Association was called to order at 2.25 P.M. by President Councilman.

Dr. Stockton read a paper entitled "Abdominal Pain from Unsuspected Irritation of the Internal Inguinal Ring," which was discussed by Drs. Cary, Peabody, Bond, Dock and Stockton.

Dr. MacCallum read a paper entitled "The Mechanism of Exophthalmos," which was not discussed.

Dr. Futcher read a paper entitled "Diabetes Insipidus," which was discussed by Drs. Baumgarten, Thompson, Tyson, Dock, Jacobi and Futcher.

Dr. Weir Mitchell read a paper entitled "A Case of Prolonged Male Hysteria, with Autopsy," which was followed by a paper on "Hysteria," by Dr. Prince. These two papers were discussed by Drs. Putnam, Mitchell and Wood.

Dr. Sachs read a paper entitled "Some Unusual Forms of Acute Myelitis," which was followed by a paper on "Infectious Myelitis." These two papers were discussed by Drs. Park, Welch, Jacobi and Sachs.

Dr. Koplik read a paper entitled "The Clinical Features, Prognosis and Treatment of Cerebrospinal Meningitis in Infants and Children," which was not discussed.

Dr. Tyson read a paper entitled "A Case of Spasmodic Stricture of the Esophagus, with Sacculation, Treated by Dilatation and Later by Gastrotomy," which was followed by a paper on "Idiopathic Dilatation of the Esophagus, Cardiospasm," by Dr. Sippy, and by the "Demonstration of a Dilated Esophagus" by Dr. Kinnicutt. These papers were discussed by Drs. Janeway and Meltzer.

Adjourned at 5.30 P.M.

WEDNESDAY, MAY 11TH.—MORNING SESSION.

The Association was called to order at 10.05 A.M. by President Councilman.

The Secretary read the nominations made by the Councillors for officers of the Association for the coming year.

The following physicians were elected to active membership: Dr. Philip King Brown, of San Francisco; Dr. Joseph Collins, of New York; Dr. David L. Edsall, of Philadelphia; Dr. Frederick Gault Finley, of Montreal; Dr. Hermon C. Gordinier, of Troy; Dr. Richard M. Pearce, of Albany; Dr. Mark W. Richardson, of Boston; Dr. Richard P. Strong, U. S. Army.

The following were elected honorary members: Dr. Beverley Robinson, of New York; Dr. Starling Loving, of Columbus, Ohio; Dr. Henry P. Walcott, of Cambridge, Mass.

Dr. Opie read a paper entitled "The Relation of Cells with Eosinophile Granulations to Bacterial Infection," which was discussed by Drs. Meltzer and Opie.

Dr. Dock read a paper entitled "A New Case of Chloroma with Leukemia, with a Study of the Cases Reported Since 1893," which was discussed by Drs. Osler, Meltzer and Dock.

Dr. Stengel read a paper entitled "Types of Splenic Anemia or Splenomegaly," which was discussed by Drs. Osler, Dock, Sippy, Cabot, Welch and Stengel.

Dr. Novy read a paper entitled "On the Cultivation, Agglutination and Filtration of Trypanosomes," which was not discussed.

Dr. Opie read a paper entitled "Zonal Necrosis of the Liver," which was not discussed.

Dr. Peabody exhibited "A Specimen of a Malignant Adenoma of the Liver," which was not discussed.

Dr. Withington read a paper entitled "Addison's Disease, With and Without Adrenal Tuberculosis," which was not discussed.

Dr. Lewis read a paper written by Dr. Longcope entitled "Experimental Arthritis and Endocarditis," which was not discussed.

During the meeting the following papers were read by title:

"Polyuria in Typhoid Fever," by James C. Wilson.

"Nephrectomy for Renal Tuberculosis," by I. N. Danforth.

"The Neoplasm Theory of Leukemia, with Report of a Case Supporting this View," by A. S. Warthin.

"Attempts to Produce Liver Necrosis by Venous Injections of Intracellular Bacterial Toxins," by R. M. Pearce and C. K. Winne, Jr.

"Pneumopericardium, with Report of a Case," by W. B. James.

"Three Cases of Probable Psittacosis," by H. F. Vickery.

"A Study of Tubercle Bacilli Isolated from Three Cases of Tuberculosis of the Mesenteric Lymph Glands," by Theobald Smith.

"Studies on the Etiology of Variola, with Demonstration of Microscopic Preparations," by William T. Howard, Jr., and Roger C. Perkins.

"Chronic Thrombosis of the Pulmonary Arteries in a Case of Multiple Serositis Simulating Aneurism of the Thoracic Aorta," by E. F. Cushing.

"Pneumococcic Arthritis," by S. Solis Cohen.

"Pulmonary Actinomycosis, with Report of a Case," by S. Solis Cohen.

"A Serious Danger in Cases of Pneumothorax," by Francis H. Williams.

"On the Etiology of Bacillary Dysentery and of Catarrhal Enteritis in Children," by G. A. Charlton and Ludwig Jehle.

The following amendments to the Constitution were presented:

Resolved, That Article II. of the Constitution be amended by inserting after the first paragraph of this article a paragraph stating: There shall be a class of "Associate Members," limited in number to twenty-five, from which class all active members shall be elected. These associate members shall enjoy all the privileges of honorary members, and each of them shall pay annual dues amounting to one-half the annual dues of an active member.

FRANK BILLINGS,
S. SOLIS COHEN,
FRANCIS P. KINNICUTT,
W. S. THAYER,
J. P. CROZER GRIFFITH.

Resolved, That the Constitution be so amended that honorary members elected or transferred hereafter shall be expected to pay annually five dollars as dues in consideration of receiving the printed TRANSACTIONS.

CHARLES G. STOCKTON,
J. P. CROZER GRIFFITH,
JAMES TYSON,
S. SOLIS COHEN,
FRANK BILLINGS.

Resolved, That the Constitution be so amended that any one who has been an active member during ten years may, at his request, be transferred by the Council to honorary membership.

HENRY HUN,
WILLIAM T. COUNCILMAN,
WILLIAM OSLER,
WILLIAM H. WELCH,
FRANK BILLINGS.

The following officers were elected:

President—Edward L. Trudeau.
Vice-President—Frank Billings.
Secretary—Henry Hun.
Recorder—Solomon Solis Cohen.
Treasurer—J. P. Crozer Griffith.
Councillor—F. Forchheimer.
Representative on Executive Committee of Congress of American Physicians and Surgeons—William Osler.
Alternate Representative—Francis H. Williams.

It was resolved that the thanks of the Association be given to President Councilman and Dr. Kober for the very successful meeting just held.

Adjourned at 1.20 P.M.

HENRY HUN,
Secretary.

ADDRESS OF THE PRESIDENT.

By W. T. COUNCILMAN, M.D.,
OF BOSTON.

Since our last meeting Dr. Israel Thorndike Dana, of Portland, Maine, has died. Dr. Dana was one of our charter members, a frequent attendant at the meetings, and an active contributor. He was a graduate of the Harvard Medical School in 1850, and after two years' study in Europe began practice in Portland, Maine, where he resided until his death. He was closely identified with all movements for the improvement of medicine in his State, an able, active man, whose death is a distinct loss to the medical profession of his State and his country.

The first meeting of our Association was in 1886. Up to that time there had been some splendid work in medical research in America, but such work was the exception. Facilities for scientific research were insufficient, and the research brought no reward.

America was late in responding to the quickening influence which the introduction of the cell theory in pathology and laboratory research had given medicine in Europe.

This Association was formed for the purpose of assembling together the men who were carrying on investigations in medicine in order that they might learn from one another, and feel mutual support and sympathy. At no period in any country has there been such rapid progress in the whole field of medicine as in the period which has elapsed. Not only have we made intelligent use of all discoveries in medicine, but the workers in America have added to the sum of the world's knowledge. I do not think any better evidence of the general advance in the

science and art of medicine is given than in the character of the program presented at the meetings of the American Medical Association and in the papers published in its *Journal*. Laboratories for the study of disease have arisen over the country, and the diligent and intelligent study leads to reward. Our medical schools have emerged from their former unenviable position and have become, or are fast becoming, medical universities.

In this advance our Association has been a prominent factor. The motives with which it started in the beginning have become recognized as the motives of all medical societies. Its example has led to the formation of other societies in fields which it formerly entirely covered, which societies are to be regarded not as rivals, but as lusty offspring. It has had presented before it the most important of the medical investigations made in the country.

It must be seen, however, that the extension of medical interest has become so great that this society cannot longer hold the same position which it held in its inception. With a limited membership it cannot include the men who are doing active work in medicine and pathology. There are numbers of young men who would formerly have been gladly welcomed for whom there is now no room. And it must include the active workers in hospitals and laboratories. Without them our meetings will have no interest. It is unreasonable to suppose that these men will be content with the presentation of their work, and the presentation of their work by another loses force. There are three ways, it seems to me, by which the difficulty may be met:

1. *Differentiation.* The society might, by giving preference in its elections to clinical men, gradually become the society for internal medicine. But a part of our strength has been that here the laboratory and the clinic meet.

2. *To Remove the Limitation of Membership.* By doing this we shall only become a rival of the American Medical Association, which is doing effective work, and, furthermore, this would certainly lead to differentiation of interests.

3. It might be possible, while retaining our active membership at the same number, to take in more new members each year. Most men probably enter this Association at the age of thirty-five

or forty years. Twenty additional years closes the most active period of life as far as production is concerned. I would suggest that active membership in the Association be limited to twenty years, after which time the member passes into the list of honorary members. As an honorary member he should have the same privilege in discussion and in the presentation of papers as the active members, and in work and speech still give his valuable assistance. This would probably give us not less than seven new members each year, which, with judicious selection, should suffice.

POLYURIA IN TYPHOID FEVER.

By M. H. FUSSELL, M.D., H. S. CARMANY, M.D.,

AND

H. HUDSON, M.D.,

OF PHILADELPHIA.

MURCHISON,[1] in his chapter on typhoid fever, says: "The quantity of urine during the first week or ten days is usually diminished. Sometimes it falls to one-half, to one-quarter, or even to one-sixth of the normal standard, notwithstanding the increase of fluid ingesta. After the second week the quantity increases, and I have frequently observed the urine to be copious, pale and of low specific gravity before the cessation of the fever. But in most cases the quantity does not increase greatly until convalescence, when the urine is almost invariably copious and of low specific gravity. At this period I have repeatedly known as many as 80 or 90 fluidounces passed in the twenty-four hours."

Arnould, in *Dictionnaire des sciences méd.*, says the quantity of urine is almost always diminished, sometimes it is more abundant, and there may be a veritable polyuria; this may be a symptom preceding the defervescence. During convalescence the urine may vary between 1500 c.c. in moderate forms of fever and 1700 c.c. in severe forms; this polyuria coincides with the more abundant excretion of the solid material of the urine. There is intimate relation between the function of the kidneys and the skin. When the patient is convalescent the polyuria corresponds with the abundant sweats; on the contrary, a dry skin and diminution of the urine is a grave sign.

One of the latest expressions on this subject is by Osler.[2] He says: "An unusual increase of urine during the progress of convalescence

[1] Contagious Fevers, third edition, edited by Cayley.

[2] Nothnagel's Encyclopedia of Practical Medicine,,American edition, edited by Osler, p. 184.

is by no means a rare manifestation; the amount may reach 10,000 c.c. and more in twenty-four hours. The urine is then remarkably light, as clear as water and of exceedingly low specific gravity down to 1002. Rarely, and then especially in nervous persons, women as well as men, this polyuria may be apparent as early as the latter portion of the febrile period."

Practically all authors of text-books are satisfied with the remark that the urine is scanty and of high specific gravity during the height of the fever and more abundant and of lower specific gravity toward and in convalescence. Some authors say that a convalescence can be practically foretold by an increase in the amount of urine of low specific gravity.

Under the caption "Polyuria in Typhoid Fever" we could discover only one article, though isolated cases have been reported and not published.

Dr. J. C. Wilson, of Philadelphia, reported a case of polyuria in typhoid fever at the section of medicine of the College of Physicians of Philadelphia, and will speak of his case in connection with this paper.

Spitz[1] reported, in 1882, under the caption "Polyuria in Typhoid Fever," a case in a patient who had a severe attack of typhoid, who passed 6000 to 8000 c.c. of urine daily during convalescence. After this observation he had the daily amount of urine of all cases of typhoid fever measured, and it was found that in about one-half of the cases polyuria was present in convalescence, he considering anything over 2000 c.c. as a polyuria. The urine was always bright yellow, free from albumin and sugar and without any sediment; it was of low specific gravity, so that it consisted mainly of water. He concludes:

1. In convalescence of typhoid fever polyuria is present in one-half of the cases.

2. The amount of urine may be increased by artificial means during severe high temperatures.

3. The increase of the amount of urine is most common in the sixth week.

4. The increase in the amount of urine is not due to any organic disease.

The case which we desire to report is as follows:

[1] Deutsche med. Wochenschrift, 1882, vol. iii. p. 107.

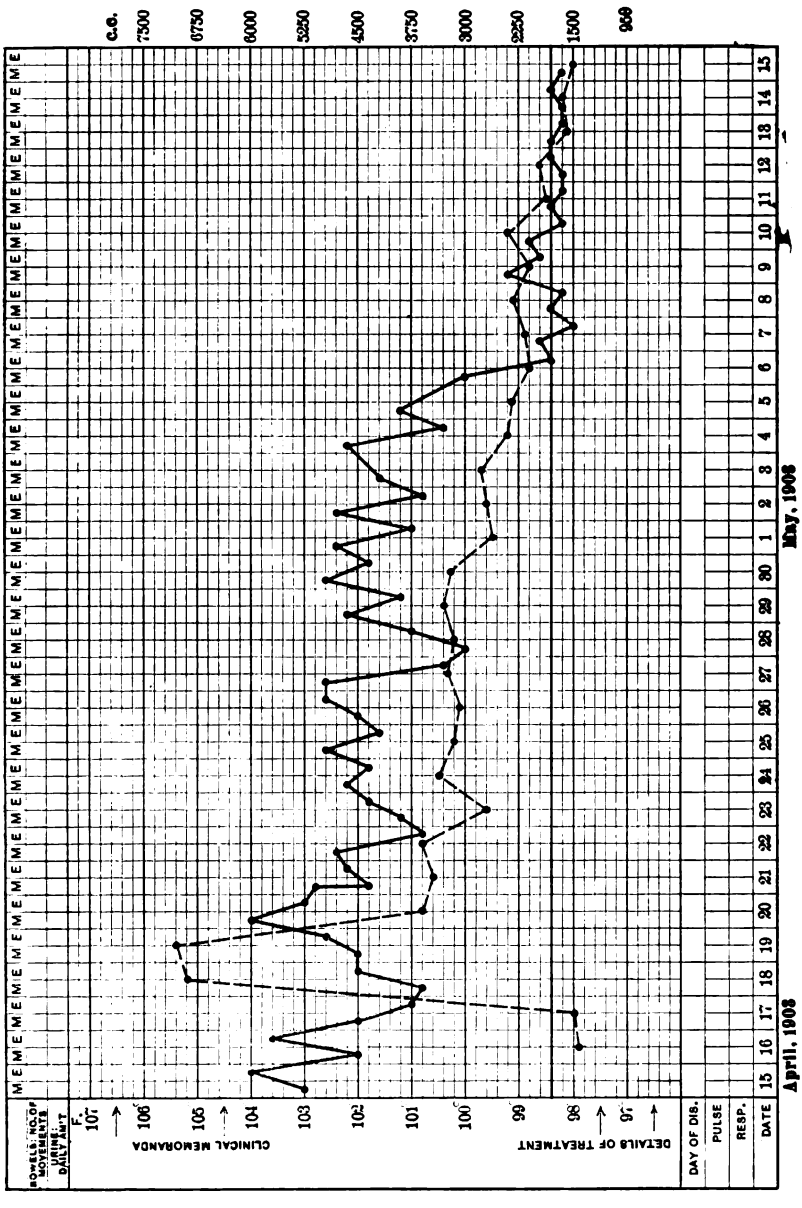
Charles S., married, aged forty years, admitted to St. Timothy's Hospital April 15, 1903, on about the eighth day of typhoid fever. The temperature on admission was 103° F. It remained between 102° and 103° until May 4th, when convalescence began.

On May 8th the temperature was normal and remained so until his discharge from the hospital. He was extremely nervous through the entire course of the disease. On April 23d, eight days after admission, he had a slight intestinal hemorrhage which had apparently no effect on the course of the disease. He was taking five grains of salol every three hours on admission, and continued this drug until April 19th, four days, when it was stopped. The first twenty-four hours after admission he passed about 1200 c.c. of urine. The second twenty-four hours he passed about the same amount. On April 18th, or the third day after admission, he passed seven quarts and nine ounces (7000 c.c.). The next day seven quarts and eighteen ounces (7200 c.c.). During this period he was nervous, but not so markedly so as later, when he was passing much less urine. He was extremely thirsty and drank water every few minutes, and passed his urine at very short intervals, in amounts varying from ten to twelve ounces. At this time the polyuria amounted to a veritable complication on account of the loss of rest and the nervous excitement which it entailed. His skin was dry, and he was restless. He was thirsty. The amount of water ingested was not measured, but he did not take an unusual amount of water before the polyuria, and the thirst diminished with disappearance of the polyuria.

On the following day (April 20th) the urine dropped to about four quarts and remained between three and four quarts (3000 c.c. and 4000 c.c.) for two days. In the next ten days he passed between two and three quarts in twenty-four hours, and he passed about the normal amount on May 13th, or almost one month after his admission to the hospital. During this period, April 15th until May 6th, his temperature ranged between 104° and normal, but the greater part of the period not being below 102°, except as the result of sponges. From May 6th to the 14th, when his temperature was normal, he passed between two and three quarts of urine daily.

It will be seen, then, that during the height of the fever he had a veritable polyuria, and as the temperature reached normal he passed decidedly *less* urine. When his polyuria was most extreme the urine had a specific gravity of 1002. On the first day it contained a trace of salicylic acid, as shown by the iron test, but only on that day; contained no albumin, no sugar, no acetone, and no diacetic acid; there was 0.004 gram of urea to 1 c.c. of urine, or 0.4 per cent. He thus passed 28.8 grams of urea, which is not far from normal. As the specific gravity rose and the quantity of urine decreased the urea percentage rose, he thus at all times passed about a normal percentage of urea. When his urine fell to three quarts the specific gravity rose to 1010, and remained at about 1010 until convalescence was fully established. At no time was there any albumin or sugar or at any time were there any formed elements. On April 11, 1904, one

CHART I.


c.c.
7500
6750
6000
5250
4500
3750
3000
2250
1500
750
F.
107
106
105
104
103
102
101
100
99
98
97
CLINICAL MEMORANDA
DETAILS OF TREATMENT
BOWELS: NO. OF MOVEMENTS IN THE DAILY LIMIT
DAY OF DIS.
PULSE
RESP.
DATE
15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
April, 1908
May, 1908
Temperature — — — Urine — — — —

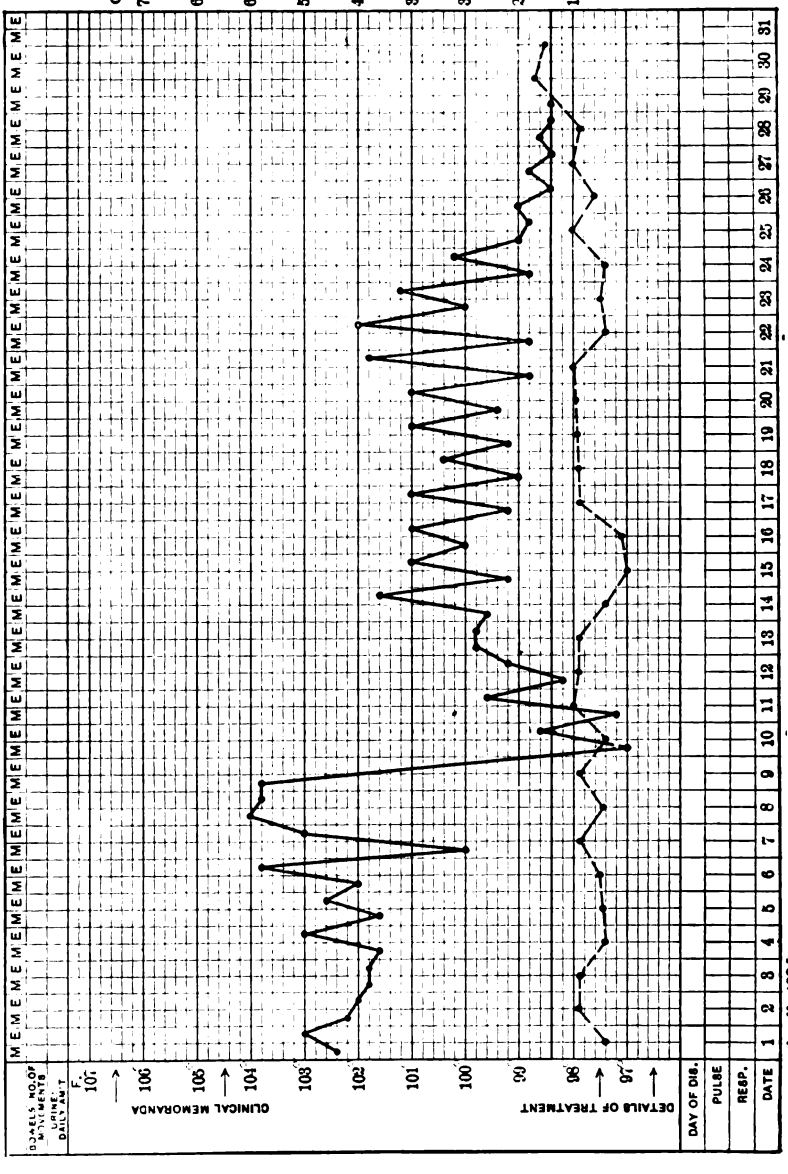
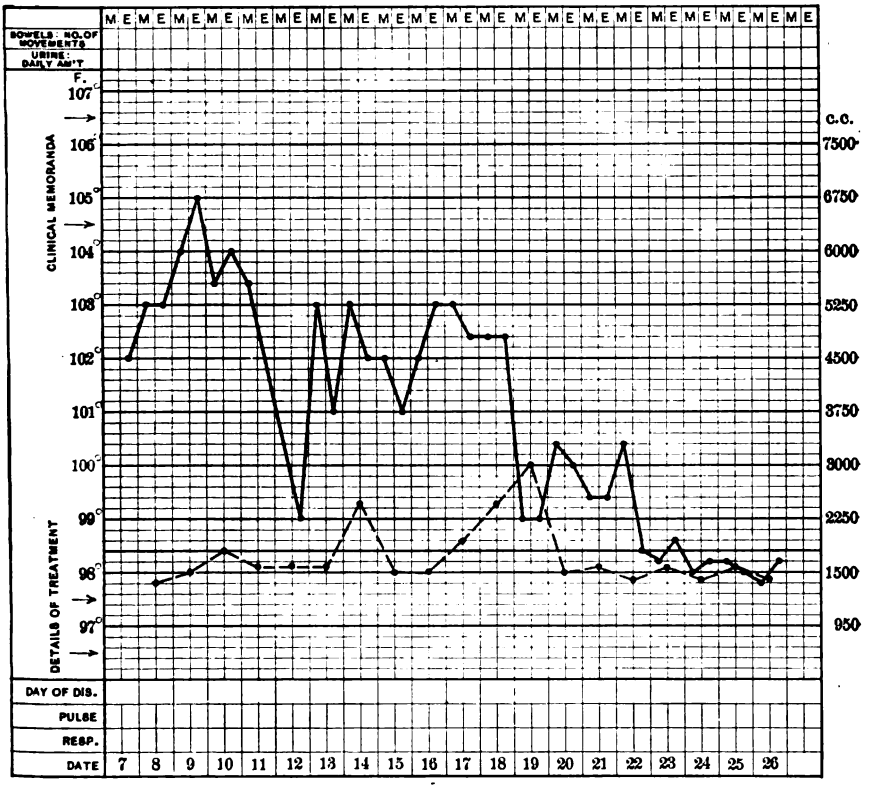

BOWELS. NO. OF MOVEMENTS
URINE. DAILY AMT.
c.c.
7500
6750
6000
5250
4500
3750
3000
1500
750
F.
107
106
105
104
103
102
101
100
99
98
97
CLINICAL MEMORANDA
DETAILS OF TREATMENT
DAY OF DIS.
PULSE
RESP.
DATE
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31
April, 1894
Temperature —— —— ——
Urine - - - - - - -

CHART II.

year after his typhoid fever, an examination of his urine was made and it was found to be absolutely normal. He is in perfect health. On three days (April 23, 24 and 25, 1904) he passed respectively 41½, 41¾ and 43½ fluidounces of urine. On April 26 and 27, 1904 (that is, just one year after his attack), he was given 5 grains of salol every three hours, and passed on each day 54 ounces and 52 ounces respectively; specific gravity 1026, otherwise negative, containing 2 per cent. urea.

CHART III.



Temperature —— —— —— Urine – – – – – –

It will be seen on reviewing this case that it differs from practically all of the cases of polyuria in typhoid fever mentioned by writers, in the fact that the polyuria began suddenly in the second week of the disease, and that the urine was greatest in amount during the height of the fever and declined as convalescence began,

and when convalescence was established the urine was absolutely normal in quantity and in character.

The polyuria spoken of by authors occurs just before or during convalescence. In order to compare the amount of urine passed in this case with the amount passed in the ordinary case of typhoid we have selected two cases of typhoid in which the urine was measured daily, one case (Ed. Dowling) where daily measurement was made for four weeks and the urine never rose above 62 ounces in the twenty-four hours, and was often as low as 12 ounces. In only one other case, besides the one quoted in this series of 180 cases, was there any excessive amount of urine passed during the height of the fever, and in that case it did not rise above 3000 c.c. in twenty-four hours. The amounts passed in this case will be seen by the charts, together with the range of temperature.

We have gone over the records of a series of cases in St. Timothy's Hospital with a view of proving the frequency with which polyuria occurred during the course or in the convalescence of typhoid fever, and in 180 cases, in which the urine was measured every day, we have discovered only 22 in which the urine was 2000 c.c. or over, and in only one of these, the one above reported, was the polyuria constant from the beginning of the disease, and in no other case except this was there a very excessive amount, 3000 c.c. being the limit.

In the great majority of the cases it was scanty during the height of the fever and rose only during convalescence; if, therefore, this series is reliable, and the measurements were made without any thought of the subject of polyuria, it would seem that the incidence of polyuria in convalescence is not nearly as common as most writers think; only 8 per cent. of our cases showed a polyuria at any time, instead of 50 per cent., as Spitz has stated in his paper, and instead of being almost without exception in convalescence, as stated by Murchison.

As to the cause of the polyuria existing in this most remarkable case which we have reported, certainly the polyuria was not due to a pre-existing diabetes on admission, as for two days the amount of urine was normal, it fell to normal with convalescence, and has probably remained so ever since, as it certainly is, as stated above, at the present writing. It was not due to any organic condition of the kidneys, because the urine has always been, even during the

existence of the passage of a great amount, normal so far as albumin and formed elements are concerned.

There would seem to remain of the ordinary causes of polyuria but two, the administration of salol and the nervous condition of the patient. The salol was stopped on the second day of polyuria, but the abnormal amount of urine continued for almost one month after the discontinuance of the drug. The patient was nervous, it is true, but when he was passing the greatest amount of urine he was much less nervous than later, when he was passing from three to four quarts. The patient was not given the bath treatment. He was under treatment in a private room, and by direction of his physician was sponged at the temperature of 103° or over. It is quite within the range of possibility that these cold sponges may have had somewhat to do with the polyuria, but it seems scarcely possible, because he received eleven sponges before the polyuria developed, and the polyuria continued eleven days after the sponges were discontinued, although in gradually diminishing amount. As to the cause of polyuria in general this paper cannot deal. The most common causes given by authorities, however, are nervousness and some organic change, either in the nervous system or in the kidneys themselves; certainly the last two were not active in this case, and it would seem that the unusual amount of urine was caused either by the very moderate use of cold water or by the unusual nervous, almost hysteric, condition in which the patient was continually. We conclude:

1. That the urine during the course of typhoid fever is usually of high specific gravity and in amount below 1500 c.c. in twenty-four hours.

2. In convalescence the amount of urine may rise in a small percentage of cases to 2000, or even to 10,000 c.c., in twenty-four hours.

3. That in very rare cases there may be a true polyuria from 3000 to 8000 c.c. in the twenty-four hours during the entire course of the disease and falling to normal during convalescence.

DISCUSSION.

DR. DOCK: This interesting case brings up a number of important points. In the first place it will be remembered that considerable work has been done on the excretion of water in fevers, especially typhoid fever, and although there are opposing results, the weight of opinion is that in the early days of typhoid fever there is actual retention of ingested water. Later, in the decline of fever, there is a polyuria that may reach an extreme degree, up to 10 or 12 liters. These observations, of course, oppose the common theory and the practice based on it, of "washing out" the bodies of fever patients. I became interested in the subject when I began to use cold baths in typhoid fever, for I noticed that there was not only no retention in the early period, but on the contrary the urine, excreted in large quantities, was of relatively normal specific gravity. This supports the washing-out theory, and I have explained the difference by the stimulation of the heart by the cold baths. I would like to ask Dr. Fussell whether any observations were made upon the blood pressure in this case. There are, of course, other factors not so easy to explain, such as the osmotic pressure of the urine and the relations of the salts.

DR. W. GILMAN THOMPSON: I would like to ask Dr. Fussell in regard to any emaciation that might have occurred in this patient and as to the amount of fluid taken by the patient. The passage of more than 150 ounces of urine in typhoid fever is not uncommon, and we observe it even in patients that have maintained good condition throughout the disease. It will be interesting also to know whether this patient had ever previously had a condition of polyuria. The ordinary polyuria is one that occurs during convalescence or in the last week of the fever, but this occurred on the second or third day.

DR. CABOT: I want to ask if the doctor thinks this polyuria had any connection with the typhoid.

DR. WITHINGTON: I would like to ask if the hysteric symptoms spoken of preceded the polyuria.

DR. OSLER: May not this polyuria be due to local irritation of the glands, as in the polyuria of tuberculous peritonitis, abdominal aneurysm and other abdominal tumors.

DR. FUSSELL: In answer to the questions, I would say first that no observation was made on the blood pressure. As to the fluid ingested, when the patient passed a large quantity of water he was drinking a great deal, but as the amount of urine decreased he ceased drinking so much. The thirst appeared

rather the result than the cause of the polyuria. He was not markedly emaciated, and at no time did he seem to be more seriously ill than the average typhoid patient. There was no previous polyuria so far as we were able to discover; he did not have the condition when he first came in, and we know that he has not had it since. He had always been nervous from the beginning, but at the time when he was passing seven quarts of urine he was much less hysteric than when only passing four quarts. Whether there was any actual relation to the typhoid, I should say yes.

A POSSIBLE CAUSE OF HIGH-TENSION PULSE IN NEPHRITIS.

By W. H. THOMSON, M.D.,
OF NEW YORK CITY.

In a patient whom I saw in consultation some years ago in a condition of status epilepticus induced by acute alcoholism, I found a pulse of high tension unequalled in my experience except in some cases of puerperal eclampsia. He was a healthy man with perfectly healthy arteries, but now those vessels were so universally and extraordinarily contracted that it seemed as if his heart were beating against one and the same well-nigh insuperable obstruction wherever a pulse could be felt. Such excessive arterial ischemia is certainly a striking phenomenon, and its mode of production is worthy of special investigation. Without doubt it can be ascribed only to the activity of some powerful vasoconstricting agent, but this can scarcely operate solely by stimulation of the vasoconstrictor nerves and indicates rather a direct action on the arterial muscular tissue itself. This case, therefore, first suggested to me to make an examination into the conditions which lead to arterial tension in general, and particularly in renal affections, with the special purpose of determining in them the date of its ocurrence.

I now feel assured that a high-tension pulse is not only one of the most persistent accompaniments of many forms of kidney disease, but that it sets in too soon to be primarily the result of any change whatever in arterial texture, just as no muscular cramp is primarily due to a textural change in the muscle cramped. In other words, high-tension pulse in nephritis is originally due to a general cramp of the muscular layer of the arterial walls, which cramp continues so long as the specific excitant of the muscular coat continues to circulate in the blood.

But while the early development of high tension in acute nephritis seems to imply the rapid charging of the blood with such an agent,

its subsequent persistence, according to the persistence of the nephritis itself, raises other questions of high interest. In repeated instances of an acute, gradually changing into a chronic, nephritis, I have found the tension remain all along just the same as at first, while in cases which recover increased tension is quite the last symptom to disappear. Therefore, if high pressure can be assigned as a leading factor in producing changes in the arterial walls, ranging from endarteritis to atheromatous degeneration, that factor of strain is present from the very beginning of the renal disorder rather than as a late consequence thereof. This has led me to reverse the steps in the etiology of many common forms of arterial degenerations, so that instead of regarding endarteritis, as I formerly did, as the cause of high-tension pulse, it is rather high tension which causes the endarteritis, of course most signally in the arterioles. I now believe in this being the true order in the genesis of most vascular sclerotic changes, and that we possibly have been misled by the coexistence of high tension with extensive endarteritis obliterans into regarding this symptom as generally the simple mechanical result of channels blocked by gross alterations in their walls. That after such organic changes have actually occurred the accessible arteries will be found overfull and tense goes without saying; but what we would emphasize is that the arterial ischemia antedates the sclerosis and owns quite another cause for its production.

Another deduction from this premise seems to me to be highly probable. If as a concomitant of nephritis an agent be circulating in the blood with the property of inducing universal arterial constriction, the consequent strain on the left ventricle of the heart must be much greater than would be caused by any mere discrete, though extensive, changes in the walls of the main arteries. Such changes we often find in senile arteries, without accompanying pronounced cardiac hypertrophy or dilatation. But I cannot conceive of a more certain cause of increased labor for the heart, with all which that fact would entail, than the presence of an agent which induces a prolonged narrowing of every artery and arteriole the body over. Moreover, it seems very probable that such a generally acting agent may alone cause sudden or acute dilatation of the heart, as I have noted in a number of instances when the most typical symptoms of acute dilatation went along with high-tension pulse in arteries which were everywhere contracted, but nevertheless perfectly

smooth throughout. In one of the most striking examples of the kind, the most careful palpation of the accessible arteries failed to show the least signs of tortuousness of the vessels or of atheromatous changes in their coats.

What the actual nature of this agent is, and whether it be produced in the kidneys themselves or in some other organs, must at present be wholly conjectural. However, the now familiar physiologic properties of the internal secretion of the adrenals, those glands which are topically so closely related to the kidneys, offer a remarkably close parallel in every particular to the apparent properties of the tension-producing agent in nephritis. The first fact which we would advert to is the extraordinary minuteness of the dose of suprarenal extract which is capable of exciting universal arterial contraction, amounting, according to Schäffer, to only $\frac{1}{800}$ of a grain in an adult man. All experimenters also agree that the active principle, or adrenalin, does not act on the arteries through their nervous mechanism, but directly upon their musculature, and that even skeletal muscles do not escape its operation. Its action upon the heart is also very specific, and if the vagi be cut or paralyzed by atropin, the heart's action becomes so violent, and the rise in tension is so enormous, as to suggest the question whether a like combination of a vagus-paralyzing poison with excess of adrenalin may not occur in those grave crises which we encounter in puerperal eclampsia.

Another suggestive fact derived from experimental researches, first fully described by Oliver[1] and confirmed by Schäffer, Vincent and others, is in Oliver's words the enormous diminution produced by suprarenal extract in the volume of the kidney in Roy's oncometer. This condition of the kidney cannot fail materially to interfere with its secretory functions, particularly in its elimination of urea, and I feel convinced that the diminution in the average daily output of urea in cases of kidney disease characterized by persistent high-tension pulse may be assigned with much probability to this cause.

Before reaching this conclusion, however, certain clinical facts should be taken into account. A decrease in the average normal excretion of urea is no criterion of either the degree or even of the existence of kidney disease. On the one hand, in some advanced

[1] Lancet, June, 1896, p. 1622.

cases of parenchymatous nephritis with general anasarca, abundant albuminuria and marked so-called uremic symptoms, I have found the daily percentage of excretion of urea vary but little from normal. On the other hand, I have notes of 13 patients in my private practice carefully observed, most of them for many months, in whom the daily excretion of urea has been from one-half to one-fourth what it ought to be, considering their weight, age, diet, etc., and yet in no one of them had any evidences of kidney disease, either chemical, microscopic or cardiovascular, been detectable. One and all of these patients are chronic invalids, but with symptoms characteristic of the term we vaguely name "neurasthenia," and with evidences of persistent gastrointestinal rather than of persistent renal disorders. I am inclined to ascribe their condition to deficient formation rather than to deficient elimination of urea, and I think my surmise is borne out by the results of treatment. With only one exception in the whole list the pulse is of low instead of high tension. Conversely persistent high-tension pulse may go along with free or normal excretion of urea. This I have found in gout. But, on the other hand, when nephritis becomes fully developed in gouty patients, the urea output falls as in other forms of interstitial nephritis.

These clinical facts, however, do not militate against the inference that except in gout a high-tension pulse goes with a contracted kidney, and that a contracted kidney is *pro tanto* incapable of a normal excretion of urea. If, therefore, the kidney be only functionally contracted, or partially so, and not yet too far sclerosed, the administration of an efficient vasodilator ought to be followed by an increased excretion of urea. This would furnish a palpable test, free from the uncertainties which so often surround inferences from clinical observations on the effects of drugs, for the greater or less quantity of urea is a simple fact and not a theory. Accordingly I have made a series of observations on the effects upon urea excretion of full doses of aconite, in patients with chronic kidney disease marked by high-tension pulse, and in the majority of them with accompanying cardiovascular changes. I chose aconite because I regard it as the most certain and efficient vasodilator which we possess; and in saying so I merely wish to remark that as a veteran teacher of the materia medica I have long held that laboratory experiments on animals as regards the various cardiovascular agents can scarcely set aside the conclusions from careful clinical observations on man. I venture to say that anyone who can recog-

nize high tension when it is present will find that tension yield more certainly and more permanently when the aconite dose begins to tell than by any other agent except veratrum viride or free venesection. The superiority in this respect of aconite to the nitrites is very marked, for even with erythrol tetranitrate in full doses the change in the pulse is too evanescent and too irregular to allow it to be compared with aconite in real efficiency against the chronic high tension of nephritis. Well aware that this is no occasion for adducing a series of clinical histories, I will, in conclusion, merely give the briefest outline of three illustrative cases of the effects of aconite on urea elimination.

CASE I.—A lady, aged sixty years, suddenly fainted on rising from the table, and was found by her physician with all the symptoms of acute dilatation of the heart. I first saw her in consultation in November, 1901. Merely changing her position in bed caused cyanosis and vertigo. I found the left ventricle much dilated, the heart impulse could not be felt, at the apex the sounds were very indistinct, while the aortic second sound was accentuated. The radials and other arteries felt perfectly smooth, but very small, and the pulse was of high tension. Every variety of vasodilators and of heart stimulants were administered perseveringly for two months, such as the nitrites, including erythrol tetranitrate, along with strychnin, caffein, spartein, strophanthus and digitalin, besides sodium iodide, arsenic and tincture of iron, but without avail. The patient continued unable to have her head raised, while uremic gastrointestinal symptoms developed, with alarming attacks of dyspnea and syncope, mild delirium, pains in the head and twitchings of the muscles of the face and extremities. The urine continued to be deficient in amount, and the daily output of urea, which was constantly estimated by her physician, amounted to only 8 grams the day before I recommended that all the other medication be stopped and the tincture of aconite in 5-drop doses be given every three hours day and night. Her physician, in a note to me, says of her subsequent history: "In a few days improvement in all her symptoms was perceptible; her digestion became better; mental and nervous symptoms disappeared; the arterial tension disappeared; the daily output of urea rose from 8 grams to 32 grams; the character of the heart action improved; the apex impulse became perceptible and slowly increased in force, and the pulse became regular and fuller. Within a week the patient sat up, supported by a bed-rack, for ten minutes, without marked change in the pulse."

The aconite was continued for six months in the same doses. The patient slowly improved, and sat out of bed from six to eight hours daily, going out to drive and taking other gentle exercise. Twice the dose of aconite was reduced but the return of high tension and diminution of the urea output to 13.5 grams

daily, with return of symptoms of cardiac weakness, caused the resumption of the original dosage.

At the end of six months the aconite was discontinued, and the nitrites were substituted for it for one month. Cardiac weakness and high tension developed again, and the urea fell to 10 grams daily. Aconite was again substituted for the nitrites, and again the heart action and pulse improved, arterial tension lessened and the urea increased to 30 grams. After four months more the aconite was discontinued, as vasodilators seemed to be no longer indicated. The patient continues to lead a carefully regulated life, makes and receives visits, takes walks and drives and has steadily improved in strength and appearance; which improvement has continued to the present time, three and a half years after her first illness.

CASE II.—J. M., aged twenty-two years, admitted to the Roosevelt Hospital first in July, 1902, in a state of coma preceded by convulsions. He remained in the hospital treated for chronic Bright's disease until January 13, 1903, when he was discharged "improved." Readmitted after a week for severe headache and vomiting, and remained from January 21st to April 4th. The last two examinations of his daily urea excretion during this latter stay were 12.5 and 7.3 grams. Readmitted May 14, 1903, when I examined him. Patient very anemic and emaciated, heart impulse weak and very diffuse, widely visible above nipple; apex beat five inches from midline in sixth space; apex systolic murmur transmitted to left; marked accentuation of both basic sounds; fine rales over both bases. Orthopnea; arteries thickened; pulse high tension, 132, irregular. Moderate albumin in urine, but full of hyaline and granular casts. Owing to his frequent vomiting no medication of any kind given, except the tincture of aconite, 5 drops, every three hours. The output of urea that day was 8.1 grams. The urea excretion gradually rose in fifteen days to 23 grams, and the casts disappeared. The aconite was then increased to 8 drops every three hours, and eight days afterward the urea stood at 28 grams, with no albumin or casts. The heart impulse had receded to just within the nipple. On June 9th, however, twenty-five days after beginning the aconite, he had an attack of vomiting and of diarrhea, induced apparently by eating articles surreptitiously brought by his friends, whereupon the urine dropped from 66 ounces the day before to 22 ounces, the urea from 28 grams to 7 grams, with much albumin and casts, and in two days he succumbed.

CASE III.—A young man, J. F., aged twenty-four years, with advanced symptoms of two years' standing of cardiovascular changes, headaches, dyspnea and repeated epistaxis; increased heart action, with orthopnea, thickened arteries, high-tension pulse; no edema. Urine: heavy cloud of albumin; many hyaline and granular casts; urea, 15.5 grams. When put on tincture of aconite, 5 drops every three hours, in thirteen days the urea rose to 40.3 grams, the albumin diminished to a faint trace, the casts disappeared, the headaches and epistaxis ceased and the dyspnoea was relieved. After taking the aconite for

twenty-seven days it was left off altogether to note the effect. For fifteen days thereafter the urea output remained high, but the headaches, epistaxis, albumin and casts returned, though $\frac{1}{50}$-grain doses of nitroglycerin were freely administered. For the next twenty days the urea output was slowly but steadily diminishing, when suddenly, thirty-six days after discontinuing the aconite, the urine diminished to 26 ounces, the urea dropped to 6.2 grams, with increased albumin and casts. The nitroglycerin was then pushed for three days more, given hypodermically in $\frac{1}{50}$-grain doses every two hours; the third day after this the urea was 10.5 grams, with no improvement. All his old symptoms were returning, and his heart action became very heaving. He was then put on aconite as before, every three hours, and in five days his urine rose to 68 ounces and the urea to 39.1 grams. After this improvement he could not be persuaded to remain longer in the hospital for further experiment.

It should be stated that in all three of these patients the diet was restricted, milk being the leading article of food.

Besides other hospital cases which I could adduce if there were time, I have full notes of patients in my private practice in whom similar results as regards increased elimination of urea were attained. In some of them it took a week before any definite change was noted. Usually in the second week the urea excretion may become double, triple or quadruple what it was in the first week, and the excretion remain for a time, as in Case II., higher than normal, considering the diet, age, sex and weight of the patient.

In some of my private patients who have taken the aconite for a number of months, or for a year, the urea gradually falls to about what would be the normal average for that patient, when I advise its discontinuance and the effect watched, for more than once the urea elimination has fallen so that the aconite had to be resumed to restore it to its proper figure.

As previously remarked, this effect of aconite on urea excretion I have found most marked in cases of chronic interstitial nephritis with cardiovascular changes, especially in patients not too far advanced in life. In elderly patients, with extensive endarteritis obliterans and high-tension pulse, no vasodilator can be expected to relieve the ischemia in vessels which have practically ceased to exist, and aconite has to be used in them with caution owing to its direct effect on the heart. Yet even in them, if tachycardia be present, a temporary administration of aconite is sometimes apparently very beneficial.

Should my observations on increased urea elimination following

on the administration of aconite in kidney disease be confirmed by others, this drug may prove to be a serviceable prophylactic against arterial sclerosis. I am also at present testing its effect on the high-tension pulse of melancholia in the inmates of two large asylums, as in melancholia also as a class the output of urea is low, but my observations are too recent to report the results. In one private patient insane for eighteen months, with very high tension, but with no kidney disease, the urea elimination has risen in five weeks from 6.2 grams to 20.69 grams, with a distinct though moderate improvement in the mental symptoms.

DISCUSSION.

DR. PEABODY: I would like to say, without reference to the conclusions, that there is no doubt in my opinion that the administration of aconite in these cases, and even in some cases where the arterial tension is abnormally low, will very materially increase the urea output. What the reasons for it are I am unable to say.

DR. THOMSON: In *Presse Medicale* of Paris, in a recent number, it is reported that the use of adrenalin in rabbits gives experimental results bearing out the view I expressed.

MEASUREMENTS OF BLOOD PRESSURE IN FEVERS BEFORE, DURING AND AFTER THE ADMINISTRATION OF STRYCHNIN.

By RICHARD C. CABOT, M.D.,
OF BOSTON.

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1. The cases included in this study were all febrile. Among them were 31 cases of typhoid fever, 4 of pneumonia, and 15 others with a variety of diagnoses.

2. In 32 cases the strychnin was given by mouth, and in 18 subcutaneously. The total daily dose was usually $\frac{1}{3}$ grain, sometimes $\frac{1}{6}$ grain. Except in a few instances the diet and position of the patient remained the same throughout the experiment.

3. The records were continued for days and occasionally for weeks before and after the drug was given, in order that the regular range of variation in the blood pressure might be ascertained.

4. The measurements were taken with Stanton's modification of the Riva-Rocci instrument. The maximum pressure was recorded as the height of the mercury column at the moment of the disappearance of the radial pulse, and the minimum as the trough of the wave of greatest oscillation of the column.

5. The measurements were taken at various intervals of time succeeding the administration of the strychnin—from a few minutes to several hours. The observations extended over about eight months, and include over five thousand measurements.

6. The total result is negative. I have been unable to convince myself that strychnin exerts any influence upon the blood pressure of febrile cases when given in manner and dose above mentioned.

7. In the twenty-four hours following the administration of the drug there was a rise of 5 mm. or more of pressure in 16 cases, a fall in 17 cases, and no change in 24. The average pressure in the 50 cases that received a daily dose of strychnin was no greater than in 18 control cases without any drug.

8. To me one of the most striking features of the investigation was the fact that while strychnin and whiskey seemed to be entirely without influence upon the blood pressures, the sight of the dinner tray or the prospect of sitting up produced a most obvious, though transient, rise in the pressure. The only permanent gains in pressure occurred when the patient reached a crisis (as in pneumonia) or when convalescence enabled him to get up and walk.

9. As in the alcohol research of last year, I do not wish to be construed as saying that the drug under investigation is of no value. To prove so general a negative my work is altogether insufficient. My conclusion is that in the dosage used strychnin does not raise or in any way affect the maximum or minimum blood pressure so far as can be determined by the instrument employed. I am indebted to Mr. R. H. Brooks and Mr. David Robinson, fourth-year students at the Harvard Medical School, for assistance in carrying out the investigation.

DISCUSSION.

DR. STENGEL: In some studies of the blood pressure in typhoid fever along the same line Dr. Cabot has made, I found that the systolic pressure under the influence of emotion as well as under the influence of large doses of the drug were not infrequently increased, but the diastolic pressure was not at all substantially increased. This is in conformity with what we would expect in view of the recent work of the Leipzig school of cardiac pathologists, showing that the vasomotor depression of typhoid fever is centric in origin.

DR. HARE: Dr. Cabot's paper is of value to the general profession, for it impresses upon them the fact that strychnin is not a true cardiac stimulant. Within the past few years the profession has come to use strychnin as a cardiac stimulant with the same energy they used to use, or do use, digitalis. I am very firmly convinced that it does not act as a stimulant in typhoid or any fever, but that it simply acts like the spur or whip upon the horse. I have frequently seen cases where the physician was alarmed by the high state of the temperature and rapid pulse, and have seen that alarm allayed when this supposed stimulant was withdrawn.

It seems to me that another series of investigations of persons in good health would make this work more complete, to determine whether strychnin has any effect upon the heart in health. I am also convinced of another point that is often ignored, that is, that we speak of the heart and the general arterial system

as two different parts of the circulation, ignoring the fact that physiologists are constantly calling attention to, that the vasomotor system is controlled not only by the medullary center but by many peripheral centers. I think one of the values of the cold bath is its influence upon the nerve supply of the local areas, and that perhaps strychnin acts in somewhat the same way in that it equalizes the circulation.

DR. CABOT: I would like to add one word as to the irritative action of strychnin; I was struck by the fact that the patients went on undisturbed and just as before when the strychnin was withdrawn in these cases.

ILLUMINATING-GAS POISONING.

A CLINICAL STUDY OF NINETY CASES.

By W. GILMAN THOMPSON, M.D.,
OF NEW YORK CITY.

In view of the frequency and seriousness of poisoning by illuminating gas it is a surprise that the condition has not received more attention in medical literature, for it presents a number of interesting phenomena, such as an eccentric fever, a high degree of leukocytosis and a large group of nerve symptoms, besides various practical problems. It has been my experience to meet with three fatal cases and a number of others in private practice besides many in hospital service. The conclusions herewith presented are based upon a study of 90 cases, a large proportion of which were treated at the Presbyterian Hospital in New York, in the service of my colleagues or myself. This series of 90 cases includes 12 in which autopsies were performed. None but comatose cases have been included, and of the 90 cases only 17, or 18.8 per cent., were fatal.

The lack of systematic nomenclature and co-operation in methods of securing the data of health board statistics in the large cities of this country is strikingly illustrated in an attempt to secure such data for this article; thus the condition under discussion is variously classed under such titles as "Coal-gas Poisoning," "Asphyxia," "Illuminating-gas Poisoning," "Suffocation," "Poisoning by Noxious Gases," etc. For example, in the *Philadelphia Health Board Annual Report* for 1900 I was surprised to find only 1 case under the heading "Poisoning by Illuminating Gas," until I unexpectedly, in the same document, discovered 5 more cases under the somewhat indefinite heading "Suffocation by Gas." There were doubtless other cases similarly disguised. In Boston there have been as many as 43 fatal cases in a year. In the *Baltimore*

Health Board Reports for 1900, 11 cases are recorded under the title "Asphyxia" from gas inhalation, and 16 more under "Noxious Gases," presumably illuminating gas in most instances. In Chicago in 1898 the health board reported 45 deaths from "asphyxia" by gas, and there were a few more probable cases under dubious headings. This inaccuracy of reports makes impossible any attempt to secure accurate data upon a large scale. In New York City in 1901 the health board reported 99 suicidal (42 females, 57 males) and 189 fatal non-suicidal cases of illuminating-gas poisoning, making the important total of 288. If the mortality ratio of the 90 cases of my series represents a fair average, there must be little short of 2000 cases in all occurring each year in New York City, a number which emphasizes the importance of more thorough study of the condition than it often receives. This great preponderance of cases in New York City is readily explained by the prevalence of cheap gas-fixtures and gas-stoves in the tenements, and by the large annual arrival of ignorant pauper foreigners who have never used gas, or who through poverty and nostalgia become despondent and suicidal.

In 1900 W. Sachs[1] in an important monograph collected from the entire literature references to 420 articles published up to that date upon illuminating-gas poisoning, to which Alexander Panski[2] added 6 more, bringing the list up to March 16, 1902. Many of these articles, however, are reports either of isolated cases or of purely experimental research. A few small series of cases have been published, but in so far as I am aware the present series is the most extensive from which an attempt has been made to draw comparative clinical deductions.

The chief difficulty in the study of this type of poisoning lies in the impossibility of estimating the quantity of gas inhaled and the degree of its dilution, as well as the duration of the inhalation. The majority of hospital cases are brought to the hospital during the early morning hours. An ignorant, careless or drunken person goes to bed at night in a room in which there is a gas-stove or gas-jet with a loose cock or leaky pipe, the danger of which is unrecognized. Falling into a sleep, made heavy by fatigue or drunkenness, the patient without awakening becomes gradually asphyxiated, at first with a well-diluted mixture of gas and air, and later by almost

[1] Die Kohlenoxydvergiftung, etc., 1900.

[2] Neurol. Centralbl., 1902, No. 6, p. 242.

undiluted gas. As coma deepens, the loud, stertorous breathing of the patient, or the odor of gas escaping beyond the room, attracts the attention of some early riser, who gives the alarm and sends the patient to the hospital. Hence it happens that a majority of hospital patients are those who have been inhaling gas for six or eight hours in increasing strength, and who have probably already been in coma for at least four or five hours.

In several instances the careless flinging of a towel or coat over the gas-bracket just before the patient got into bed caused a reopening of a gas-cock which had been turned off. Some of the most serious cases arose in connection with the use of gas-stoves, the pipes of which usually discharge more gas than those of single illuminating burners. There are a few other cases in the series among workmen who have been suddenly asphyxiated by almost undiluted gas, or among those who, with suicidal intent, have deeply inhaled the gas from a tube and have thus suddenly been overcome by it.

Although, as above stated, it is difficult to estimate the volume of gas inhaled in the series of cases reported, enough had been taken in almost every instance to render the patient comatose for at least an hour, if not much longer, after discovery. The minor effects of chronic gas poisoning in slight degree such as anemia, vertigo, various forms of indigestion, muscular weakness, etc., will not be dealt with in this discussion. Among the 90 cases of the series 12 patients were definitely known to have attempted suicide, and there were probably as many more who, upon recovery, were unwilling to acknowledge it. This is rendered the more probable from the preponderance of young women among the patients. The patients comprise 53 females and 37 males, and their ages ranged from four months to seventy years.

In most cases of this series ordinary illuminating gas was inhaled, containing certain volatile hydrocarbons besides from 5 to 10 per cent. of carbon monoxid, but in some cases water gas was inhaled containing 20 to 30 per cent. of CO. It has been shown experimentally that 0.10 of 1 per cent. of CO, when inhaled, causes discomfort, restlessness and dyspnea, and between 1 and 2 per cent. may be fatal if inhaled pure. It is well known that gas forms a relatively stable compound with the hemoglobin of the blood, thus markedly interfering with the oxygen-carrying power of the red corpuscles; but it also possesses a second, more important, direct

toxic effect upon the central nervous system, of the nature of a narcotic and depressant. That it causes a displacement of the nascent oxygen of the red cells and thereby deprives the tissues and nerve centers of the body of oxygen is not a sufficient explanation of the clinical phenomena of illuminating-gas poisoning. These phenomena, especially those emanating from the nervous system, are too complex to be accounted for otherwise than through some specific toxic influence of the gas itself upon the central nervous system. Moreover, these symptoms appear in cases in which there is still a large percentage of red cells unaffected by CO, and they often persist long after all CO has left the blood. For example, in *Case* 43 the red cells on the sixth day numbered 5,440,000 and the hemoglobin was 95 per cent., yet the patient died two days later with apparently normal lungs as well as normal blood. In *Case* 46 on the eighth day the red cells numbered 5,400,000 and the hemoglobin was 95 per cent. On the twenty-first day the red cells were 4,944,000 and the hemoglobin was 100 per cent., but the fever, leukocytosis (18,200), and a feeble mental state still existed. That the hemoglobin at this date was normal was proved by spectroscopic examination.

The leukocytosis is a very important symptom. Most of the cases came under observation before the value of differential counts was appreciated, and some of them before even a general leukocyte count was in vogue, hence I am unable to offer differential counts. A general count was made in 29 cases, in all but 2 of which a considerable increase above the normal was observed. In 18 of the 29 cases a leukocytosis above 18,000 was determined. Among adults the highest non-fatal cases registered respectively 44,000, 32,000 and 31,000.

In the mild case of an infant of four months the count was 52,000, but it is normally high in infancy. It is an interesting fact that in every fatal case in which a leukocyte count was made it exceeded 18,000, the two highest counts being each 50,000. The maximum leukocytosis is usually attained within the first twenty-four hours, but sometimes not for forty-eight hours. Afterward it subsides slowly, and in the more severe cases it persists more than a week and outlasts the coma and many other symptoms. A leukocyte count above 18,000 or 20,000 is always a symptom of grave import, although it does not make the prognosis necessarily fatal, and even in fatal cases there may be a gradual subsidence of the number of

white cells, as illustrated by *Case* 58, in which the leukocytes on succeeding days were counted as follows, commencing with the first: (1) 50,000, (2) 38,500, (3) 14,300, (4) 14,200, (5) 13,800, (6) 13,800. This patient died on the sixth day, from bronchopneumonia. The following cases are cited in support of the above statements:

Case 33. Admission count 22,000. Six days later leukocytosis 11,300, yet the coma lasted only eight hours and the temperature did not rise above 101.5° F.

Case 46. Leukocytosis lasted twenty-one days, during which time the patient remained either comatose or delirious and the maximum temperature was 103° F. The maximum leukocyte count was 21,800 and the minimum 13,800. The red cells and hemoglobin percentage, first estimated on the sixth day, remained normal.

Case 45. The admission count was 14,600. The following day it fell to 7700 and the patient recovered.

Case 4. The admission count was 44,000; two days later it fell to 15,000; coma lasted only one day, and the temperature did not exceed 101.5° F. On the sixth day the patient recovered.

Case 62. This patient was comatose for only three hours after the time of first exposure to the gas, yet the leukocyte count was 14,000. A differential count showed: polymorphonuclear cells, 92.3 per cent.; lymphocytes, 3.3 per cent.; large mononuclear cells, 4.1 per cent.; eosinophiles, 0.3 per cent.

Case 31. The admission count was 13,500; the following day it rose to 21,000 and the patient died in coma on the fourth day.

In explaining the leukocytosis no doubt some allowance should be made for the stasis in the peripheral vessels accompanying cyanosis, but that this is not the sole cause is demonstrated by the fact that it is observed in mild cases with vigorous pulse and no cyanosis, and in other cases it persists after cyanosis has disappeared. It certainly does not accompany, as in hemorrhage, a numerical loss of the red cells, for they remain normal in number, and, moreover, it often exceeds in degree the leukocytosis of that condition. It would appear to be a justifiable conclusion that it is due to some specific action of the gas, such as may occur in ptomaine poisoning. (In a case of the latter toxemia I have records of leukocytosis exceeding 15,000.) I am indebted to Dr. Herbert S. Carter for an analysis of the chlorids and urea of the blood in 5 non-fatal cases. According to Halliburton[1] the average percentage of chlorids in

[1] Text-book of Physical and Pathological Chemistry, p. 61.

normal blood is: sodium chlorids, 0.27; potassium chlorid, 0.205; total chlorids, 0.475.

In Carter's cases the total percentage was as follows: (1) 2.5, (2) 1.4, (3) 1.01, (4) 0.62 ,(5) 0.57, showing a considerable increase in several instances.

According to Halliburton[1] the urea percentage of normal blood lies between 0.02 and 0.04, whereas in 4 of Carter's cases the analyses gave (1) 0.063, (2) 0.057, (3) 0.05, and 0.037, respectively.

The temperature of the body is elevated in almost all the unconscious cases, and fever lasts from one day to a week or more, the average duration being about three days. The temperature does not afford a definite index of the severity of the case, for there may be a low temperature with coma as in *Case* 6, in which the temperature did not rise above 100° F., although the patient remained unconscious four hours after being brought to the hospital, or there may be a high temperature with normal consciousness. In 8 cases there was a preliminary fall before the rise of the temperature, as shown in the following group:

Case 6. The admission temperature was 97° F., but the pulse was 120 and respirations 28. Subsequently the temperature rose to 100° F., with the same rate of pulse and respiration.

Case 8, in which the patient's admission record was: temperature, 96.4° F.; pulse, 126; respirations, 30. In this case the maximum temperature, 101.5° F., was attained on the second day, but the pulse rate fell to 84 and the respiration to 20. Unconsciousness lasted one hour after admission. In *Case* 9, although deep coma lasted for ten hours, the admission record was: temperature, 99° F.; pulse, 150; respirations, 30; and the maximum temperature attained on the evening of the first day was 100.2° F.

Case 18. The admission temperature was 96.5° F.; pulse, 92; respirations, 26. Within six hours the temperature rose to 101.5° F.; pulse, 140; respirations, 40; and the next morning the temperature became subnormal.

Case 25 was that of an infant of four months. The child's nurse was playing with it when she discovered a strong odor of gas and fell unconscious. She soon recovered, but the infant continued unconscious for about half a day. The temperature remained at 98° F., but the leukocyte count was 52,000, somewhat above the normal for an infant. Recovery was prompt.

In *Case* 50 the admission temperature was 96.5° F., and within twenty-four hours it rose to 102.8° F. After convalescence from the gas poisoning a neuritis and erysipelas developed.

[1] Loc. cit., p. 251.

Case 58. The admission temperature was 95° F.; pulse, 98; respirations, 28. During the day, and following phlebotomy and infusion, the temperature rose rapidly to 102° F., with the same rate of pulse and respiration. The temperature continued to rise for five days, when just before death it reached 107° F. The patient had been exposed all night to the gas and remained comatose throughout.

Case 60. The admission temperature was only 96° F., although the respirations were 40 and the patient remained five hours in coma before death.

Possibly subnormal initial temperature would be more often found except for the fact that most patients have been unconscious for several hours before discovery. The character of the temperature varies so much that it is difficult to construct a typical curve. Thus the maximum, usually attained on the first day, may be postponed for one or two days, and a day of normal temperature may intervene between two febrile days. Usually the temperature is remittent and the subsidence is by lysis, and in about one-third of the cases during convalescence it becomes subnormal, often falling as low as 97° or 96° F. In *Case* 15 the temperature after reaching 96° F. remained five days at 97° F.

Case 56 illustrates two causes of modification in temperature which may affect the ordinary toxic fever of gas poisoning, namely, infusion and pneumonia. The patient was admitted with a temperature of 101.8° F.; pulse, 120; respirations, 48. After a phlebotomy of 8 ounces and infusion of 1000 c.c. the temperature rose to 105.5° F. without alteration in the rate of pulse or respiration. A chill accompanied the elevation of temperature. The latter fell very rapidly 6.5° F., so that the next morning the record was 99° F., with pulse and respiration unchanged. The second day the temperature rose again to 105° F., and the patient died on the fifth day, of pneumonia.

Case 19. This patient, an ignorant foreigner, blew out the gas on retiring, being unfamiliar with its effects. He had one of the most protracted fevers of any of the uncomplicated cases recorded in this series; for nine days the temperature ranged between 100° and 102° F.; for four days more it reached 100° F., and then for two days remained subnormal, falling to 97° F. On the first day a temperature of 102° F., which would have been apparently the limit of toxemia temperature, was interrupted by the chill and elevation of temperature to 108° F., following phlebotomy (8 ounces) and infusion (1000 c.c.); the corresponding pulse was 160, respira-

tions were 56, and leukocytosis 24,300. Recovery. The vagaries of temperature are, I think, explainable on the ground of disturbance in the normal chemical processes of the body and circulatory unbalance consequent upon the altered pulse and respiration, rather than by the assumption of any specific thermogenetic action of the gas. Other gases and vapors inhaled, like the anesthetics, do not produce fevers, nor do chemical poisons as a general rule, unless they give rise to inflammation, although there are some exceptions to the latter statement; as, for example, the case of a child of two years who was admitted to the hospital within half an hour after accidentally drinking kerosene.

The admission record in this case was: temperature, 102.5° F.; pulse, 160; respirations, 60. The following day the temperature was 103° F., and the patient was drowsy and feeble, but finally recovered.

The maximum temperature recorded in any of this series (excepting *Case* 19) was 107° F. in 2 cases, both of which terminated fatally. The maximum record in any non-fatal case was 104.8° F. (*Case* 42). The maximum duration of elevated temperature in any non-complicated case was twenty-two days.

An interesting case with hyperpyrexia is reported by William A. Steel, of Philadelphia (*Philadelphia Medical Journal*, February 16, 1901). The patient was a girl eight years of age. The temperature rose rapidly after coma began and within eight hours reached 110° F., with heart beats of 215, the pulse being imperceptible. After the use of oxygen a cold plunge and vigorous hypodermic stimulation the child recovered and was discharged from the hospital cured on the fifth day.

The *pulse* is markedly accelerated and usually out of all proportion to the temperature and respiration. It is seldom below 120 and frequently reaches 136 or 140 during the coma. For example, in *Case* 24 the pulse rate was 150, while the respiration rate was 30 and the temperature only 100.2° F. During coma the pulse is usually but not invariably much weakened, but remains regular in rhythm. In other words, the pulse conveys the impression that the heart is being irritated directly or through its nerves by some specific form of poison; the acceleration is certainly not secondary to any changes in the lungs, for it is observed in many cases in which the physical examination of the lungs is entirely negative, as in *Case* 11, with a pulse of 142; nor is it due exclusively to the deprivation

of the blood of oxygen, as it exceeds in degree what would be expected under those circumstances.

The maximum pulse rate observed in any of the non-fatal cases among adults was 150.

The *respiration* is accelerated irrespective of the condition of the lungs. It averages about 30, but I have records of 12 cases in which it reached 36 or more, although physical examination of the lungs was entirely negative. It is apt to be labored or jerky in type, and with profound coma it may become of Cheyne-Stokes irregularity. This type of dyspnea occurring independently of pulmonary edema or congestion is necessarily of central origin, due either to lack of oxygen at the medullary center or probably to the direct toxic irritation there of CO or some other ingredient of the illuminating gas. The maximum rate of respiration observed in any non-fatal case of the series was 62, although it reached 80 in a fatal case. In not a few cases artificial respiration was maintained for a long time with the effect of prolonging life to recovery. In the two following cases the respiration rate was extremely slow for some time after admission.

Case 27. The patient designing suicide took the tube of a gas-stove in her mouth and inhaled the gas for ten minutes. She was found pulseless with respirations of only 5 per minute. Artificial respiration was performed and hypodermic stimulation was given; she became conscious in fifteen minutes and recovered without fever, although the pulse reached 120.

In *Case* 42 the respirations on admission were only 2 or 3 per minute, and artificial respiration was maintained for an hour. Phlebotomy and infusion were performed and the breathing improved, the rate rising to 32.

Digestive disturbances are observed, but are not severe or characteristic. Constipation is the rule, and vomiting sometimes occurs, more often in the mild cases or during convalescence from coma; it became severe in 8 cases of the series. Extreme dryness of the mouth and congestion, redness and dryness of the pharynx were observed in many cases. Several patients experienced excessive perspiration.

The *urine* presents no special peculiarities. It is often of high specific gravity, 1025 to 1032, and the proteid waste is usually somewhat increased. A heavy deposit of uric acid is common. Albuminuria was noted in 26 cases of the series. In many the albumin was represented by a mere trace; in others there was 10 per

cent. by volume, with hyaline and granular casts. As many of these cases occurred among the alcoholic or those advanced in years, it is probable that the gas has no direct influence in producing albuminuria, although it was observed in an infant of four months. In one fatal case methemoglobin was found in the urine on the first day and again on the third. In several other cases in which it was searched for it was not present.

In many cases there was retention of urine, and catheterization was often necessary, even after consciousness was regained. In the majority of cases constipation was obstinate and repeated doses of cathartics and enemata were required. In 8 cases there was incontinence of both urine and feces, in some instances persisting three or four days and outlasting the stage of coma by two or three days. In a few more cases there was incontinence of urine alone.

The *pupils* present such varied appearances that there is nothing typical about them. In fully one-fourth of the cases they appeared normal and reacted normally. In 12 cases they were distinctly enlarged, sometimes with and sometimes without reaction to light. In a half-dozen cases they were diminished; twice they were unequal in size, and in two cases there was temporary nystagmus, one presenting also lateral deviation of the eyeballs. In one or two cases a sensation of fulness and ringing in the ears was complained of, and in one instance deafness persisted for a day in one ear.

As above stated, the nerve symptoms are so varied as to force the conclusion that illuminating gas acts as a direct poison to the central nervous system, for they cannot all be accounted for upon the theory that the gas acts alone by depriving the red blood corpuscles of their ability to transport oxygen. These symptoms are tremors, muscular twitching, convulsions, rigidity opisthotonos, anesthesia, increased reflexes, headache and coma. The nerve symptoms vary with the mode of poisoning. When the patient is awake and inhales the gas slowly or well diluted he experiences headache and vertigo, often accompanied by nausea and vomiting, with muscular prostration. Evidence of vasomotor paralysis appears in burning sensation in the skin, especially of the face, and in redness of the cutaneous surface. Later the lips and extremities become bluish, although owing to the peculiar cherry-red color imparted to the blood by CO the ordinary duskiness of extreme cyanosis for some time may remain absent. It is important

to note that the degree of cyanosis is independent of any changes in the lungs such as congestion, edema, etc., and is often extreme while the lungs remain normal. The patient meanwhile experiences visual disturbances, confusion of ideas, and becomes drowsy, perhaps delirious, anesthetic and finally comatose. In cases in which the patient is poisoned while asleep or under the influence of alcohol, or in cases in which a large quantity of the concentrated gas is at once inhaled, the preliminary nervous phenomena above mentioned are absent and the patient passes at once into coma without wakening. The coma, which is always profound, is usually accompanied by loud stertorous breathing and sometimes by dilated pupils and involuntary evacuation of feces and urine. In some cases, after hours of unconsciousness, the patient may be partially aroused to take nourishment, only to relapse again. The coma may last from half an hour to many days, and it is usually accompanied, as stated above, by elevation of body temperature and a rapid, feeble pulse; but there are afebrile cases of coma, as there are cases in which it is the chief and almost the only symptom. In Hewetson's case the coma lasted nine days and was fatal. In *Case* 46 it lasted ten days. As the patient slowly regains consciousness he may suffer for days from mental weakness, dulness, and confusion, with loss of memory. Paresis or spasm of the extremities may persist for several days after coma with muscular weakness, but in the majority of cases complete recovery is fairly prompt without sequelæ.

A large number of cases have been reported in recent years in which there were interesting symptoms referable to the brain, cord and peripheral nerves—symptoms which may be well explained after a review of the reported autopsies which follow (p. 38).

Bruneau[1] reported a case of hemiplegia following gas poisoning, Finkelstein[2] one of dementia, and A. Scott[3] one of acute mania with recovery after ten days. Zieler[4] reported a case of leptomeningitis serosa; Bruns[5] reported a case of disseminated encephalomyelitis, and Alexander Panski[6] another in which the patient was ill for months with paralysis of the legs and arms, sensory and speech disturbances, amnesia and mental weakness. Becker[7] reported

[1] Thèse, Paris, 1898.
[2] Jahrb. f. Psychiatrie, 1896.
[3] Lancet, 3778.
[4] Inaugural Dissertation, 1897.
[5] Encyk. Jahrb. der gesammt. Heilk., Bd. vi., 1896.
[6] Neurol. Centralbl., 1902, No. 6, S. 242.
[7] Deut. med. Woch., 1898.

a case with multiple sclerosis. Cases with multible neuritis have been reported by Glynn,[1] Meczkowski[2] (3 cases), Skowrouski,[3] Bregman and Gruzewski[4] (6 cases) and others.

The only occasional sequelæ apart from those above described, referable to the nervous system, are bronchitis, bronchopneumonia and lobar pneumonia. Small mentions diabetes as a possible sequel; it was not noted in any of the cases of my series. Pleurisy was observed once. Tuberculous patients did not appear to suffer more than those with normal lungs.

The assertion is made by Small (*Twentieth Century Practice of Medicine*, vol. iii. p. 589) that the chance of recovery lessens with the duration of exposure to the gas and that after eight hours there is very little chance of recovery, yet this is by no means an infallible rule; for example, Hewetson reported (*Johns Hopkins Hospital Bulletin*, 1893) the case of a man who was exposed for the very brief period of three minutes to the inhalation of gas in an open trench. On immediate removal he was insensible; coma with repeated convulsions lasted for nine days, when the man died. This case is also opposed to another assertion of Small (*loc. cit.*, p. 588) that when the onset of coma is sudden it is less likely to be either profound or prolonged. It does not appear from my cases that the mode of onset of coma is of much prognostic significance. The following cases are cited in illustration:

Case 3. Male, German, aged forty-five years, became despondent through loss of work, and having complained all day of headache put an open gas-pipe in his mouth and was found unconscious a few minutes after by his wife. In the hospital he exhibited profound coma, a feeble, irregular pulse and a chest full of large, sonorous, moist rales. Respiration was of Cheyne-Stokes type, and the exhaled breath smelled strongly of gas for twelve hours. The evacuations of urine and feces were involuntary. The chest was cupped; phlebotomy was performed (8 ounces), followed by infusion (1000 c.c.). Slight improvement resulted, but profound coma persisted for four days, when the patient could be roused to take nourishment. His maximum temperature was only 100.5°; pulse, 104; respirations, 24; and leukocytes, 10,400. On the eleventh day the patient was discharged cured, although the persistence of melancholia should remind one that in suicidal cases melancholia during convalescence might be mistaken for a sequel of poisoning.

[1] British Medical Journal, 1895.
[2] Gazetta Lekarska, 1899, Nos. 48, 49.
[3] Fortschrit. der Med., 1901, No. 18.
[4] Kronika Lekarska, 1897, No. 4.

This case is interesting on the following grounds: (*a*) the sudden onset of profound coma; (*b*) the predominence of coma over all other symptoms, notably the nearly normal pulse, respiration and temperature; (*c*) the final recovery after four days of deep coma.

Cases 43, 44, 45 and 46 belonged to a series of five patients all sleeping in one room into which water-gas containing 20 per cent. of carbon monoxid escaped for about ten hours. All were equally exposed; one (*Case* 43) died after eight days, two recovered in four and five days respectively, and one (*Case* 46) remained either comatose or delirious and stupid for three weeks with a continued fever, but without pneumonia; he was finally taken home when nearly well. (The fifth patient was not brought to the hospital.)

E. H. Bartley states (Wood's *Reference Handbook of the Medical Sciences*, vol. ii. p. 215) that "when entire unconsciousness has occurred recovery is very unusual." This, to say the least, is a pessimistic view, for of the 90 cases of this series in which coma was profound 73 resulted in recovery. In 39, or more than one-half of the non-fatal cases, coma lasted one day or longer, and in 12 more it lasted half a day (twelve hours). Among the longest non-fatal coma records are the following: 1 case of ten days', 1 of four days', 4 of three days', and 4 of two days' duration.

Rigors may be persistent, but more common are general muscular tremors and twitching or spasm, which latter may finally result in violent convulsive seizures and opisthotonos. Repeated convulsions have been known to last for days. In Hewetson's case they persisted for nine days, and in some of my cases for three or four days. In 8 cases they were very severe. One patient had convulsions on the third day for the first time, but she gave a history of epilepsy and they were apparently of that origin; she recovered. Rigidity of a part or of all the skeletal muscles was very persistent in a half-dozen cases, and in one (*Case* 46) it lasted in some degree for three weeks. It was often accompanied by twitching or convulsions (recovery). The major reflexes present considerable variation. In many cases they were normal, and when altered in about equal number they were increased or diminished. During convalescence patients often complain of stiffness of the muscles and sometimes appear dazed when first attempting to walk.

A patient of Broadbent (*British Medical Journal*, May 13, 1903) improved for ten days, when rapid muscular atrophy ensued, and the asthenia culminated in death on the nineteenth day.

Phlebotomy, followed by venous infusion of normal salt solution, should be performed in every case in which the patient is unconscious and the pulse is vigorous. Infusion alone should be performed in every unconscious case in which the pulse is too feeble to justify phlebotomy. If these operations are done at all they should be thorough. It is better to withdraw 15 or 18 ounces of blood than 8 or 10 when the pulse strength permits, and at least 1500 c.c. of saline solution should be infused. The latter process may be repeated upon the opposite arm, or hypodermoclysis and saline enemata may be given. The objection sometimes raised against saline infusion that it may produce pulmonary edema is not sustained by the evidence of the series of 41 cases in which it was employed, for in no one of them did it give rise to the physical signs or postmortem finding of edema of the lungs, but, on the contrary, often relieved this condition when it was already present. Whether the phlebotomy and infusion act by removing a small portion of the poison by diluting the blood, affecting the vascular pressure by the influence of the salt infused by stimulating the formation of new red blood cells, or in some other manner, the clinical fact remains that these measures are beneficial. They do not immediately restore consciousness, but in the bedside notes of the cases herein reported it is almost invariably stated that immediately after infusion the pulse grew stronger, respiration was of a better character, muscular twitching disappeared, rigidity lessened, and the general condition of the patient improved. Of course there are many cases in which a very large dose of gas renders all curative efforts futile, but in a considerable proportion the improvement which follows phlebotomy and infusion ultimately results in recovery.

Pathologic Findings. In the succeeding 12 cases in which autopsies were performed I shall merely quote the records in so far as they concern the heart, lungs and brain, as nothing distinctive was observed in the kidneys or any other organs. For these records I am indebted to the pathologists of the Presbyterian Hospital and (for one case) to Dr. W. J. Elser.

Case 54. *Heart* muscle pale and flabby; left pleura adherent to thorax throughout; *lungs* on section both show congestion and edema throughout; *brain* appears normal.

Case 86. *Heart* presents lesions of chronic endocarditis and myocarditis; the mitral valve is irregularly thickened and there are numerous calcareous

vegetations on the aortic valve; *lungs* pale, but otherwise normal; in the *brain* a calcareous embolus is found lodged in the internal carotid artery at the origin of the middle and anterior cerebral arteries. The lodgement of this embolus explains an attack of partial hemiplegia which the patient had three months before death, and did not appear to be in any manner connected with the cause of death; the brain otherwise appeared normal.

Case 78. *Heart* presents fibrinous patches on the endocardium and fatty degeneration of the papillary muscles; the lower lobe of the right *lung* is congested and the left *lung* is edematous anteriorly; areas of bronchopneumonia involve the right upper lobe and posterior part of the left lower lobe; the *brain* exhibits atheromatous nodules in the left middle cerebral artery and congestion of the vessels of the pia, corpus callosum, and corpus striatum.

Case 80. *Heart* soft and flabby, but not dilated, filled with fluid and clotted blood; *lungs* are both slightly edematous, otherwise normal; *brain:* evidence of chronic meningitis is present, the dura mater is adherent to the calvarium, and both meninges and brain substance are much congested; the lateral ventricles contain a small quantity of bloody serum.

Case 55. *Heart* normal; *lungs:* left pleura presents patches of fibrous thickening near the base of the lung and a few petechiæ over the posterior part of the left upper lobe; the latter is edematous and congested; the left lower lobe is dark red and its posterior portion is atelectatic; the right pleura is here and there adherent; the right lung is emphesematous anteriorly, but posteriorly it is congested and edematous with areas of partial atelectasis; the *brain* substance, arachnoid and pia are all moderately congested.

Case 56. *Heart* muscle and pericardium are of a dark-reddish or purple hue; the heart is otherwise normal; *lungs:* the left upper lobe is tuberculous, the left lower lobe is congested; the right lung shows areas of emphysema, congestion and bronchopneumonia; the *brain* substance and arachnoid are congested.

Case 57. *Heart* normal excepting slight atheroma of the coronary arteries; *lungs:* the entire pleura is everywhere adherent, and the left upper lobe of the lung presents a chronic miliary tuberculosis; miliary tubercles are also scattered throughout the right lung; congestion and edema are absent; *brain* not examined.

Case 58. *Heart* muscle flabby, but the organ is otherwise normal; the right pleura is somewhat adherent; the *lungs* are normal; *brain* not examined.

Case 59. *Heart* normal; pericardium dry, but non-adherent; *lungs:* few petechiæ on entire pleura; posterior portion of left upper lobe of the lung is dark and somewhat atelectatic; right upper lobe is congested posteriorly, emphysematous anteriorly; right lower lobe somewhat atelectatic posteriorly; trachea and larynx are deeply congested; the *brain* is much congested throughout.

Case 85. The *heart* muscle is pale and flabby, the left ventricle is slightly dilated; the *lungs* are both deeply congested and show slight emphysema anteriorly; the pleura is adherent over the right upper lobe; *brain* not examined.

Case 60. *Heart* shows advanced stage of chronic endocarditis with calcareous deposit in and vegetations upon the aortic cups, a thickened mitral valve and retracted chordæ tendinæ; the heart muscle is pale and hypertrophied; the *lungs* are congested and edematous and the pleura is adherent over the right upper lobe; the *brain* tissue appears normal, but the cerebral vessels are highly atheromatous.

Case 61. The *heart* is slightly hypertrophied and filled with partially clotted, dark-red blood. The myocardium is of a pale-red, somewhat cloudy appearance; in the coronary vessels and aortic arch is a moderate grade of atheroma; the valves are normal. The *lungs* present a moderate grade of congestion and edema and in the lower lobes are foci of aspiration pneumonia; the bronchi are congested and contain an abundant serous exudate; in the pleura on both sides are about 100 c.c. of clear, serous fluid. The *brain* substance is soft and edematous; the convolutions are flattened and the meninges congested; the ventricles contain much fluid; the anterior internal portion of the left lenticular nucleus and the adjoining portion of the internal capsule exhibit an area of softening about three-quarters of an inch in diameter, which contains a number of minute capillary hemorrhages; the basilar vessels are normal.

[The notes of this autopsy were furnished by Dr. William J. Esler, from the clinic of Dr. G. L. Peabody at the New York Hospital.]

It is of some interest to note that in no one of these 12 fatal cases was there entire absence of some serious chronic lesion in either heart, lungs or brain, despite the fact that many of the patients were young. Thus chronic endocarditis, myocarditis, tuberculosis, pleuritic adhesions, atheroma, chronic meningitis, etc., testify to the ill health and lowered vitality of a class of patients whom privation and physical suffering may have driven to suicide, or whose ignorance, stupidity or alcoholism has led to fatal poisoning. The important conclusion seems justified that many of these patients might have survived the gas intoxication had not either their respiratory, circulatory or nervous mechanism been already seriously undermined.

The Heart. Of the 12 fatal cases, in 3 the heart was normal, in 3 it is described as "pale and flabby," and in 6 there was evidence of either chronic endocarditis, myocarditis or atheroma of the coronary vessels. Hence there is no constant appearance of the heart in gas poisoning. If this toxic agent caused death by direct paralysis of the heart, it might be expected to be uniformally pale and flabby and perhaps dilated, but the few cases in which these occurrences were noticed are offset by others in which it appeared normal or (as in *Case* 56) of a dark-red color.

The Lungs. It was a surprise to the writer that bronchopneumonia or other definite pulmonary lesion is not more constantly an outcome of fatal gas poisoning, but in only 3 of the 12 fatal cases was bronchopneumonia observed. I have seen it in one other private case where it followed complete recovery from the gas intoxication and ultimately proved fatal. Two other cases of this series presented normal lungs, and a third lungs which were without congestion or edema, having only a few miliary tubercles; hence it may be asserted that death from illuminating gas is not invariably due, if ever, to direct irritant action upon the lungs or bronchi after the manner of smoke or toxic vapors. The conditions which might be attributed to such action may be described as functional disturbances rather than organic changes; such are (1) congestion, complete (1 case); (2) congestion and edema, complete (3 cases); congestion and edema in partial areas (5 cases), in all 8 cases; (3) atelectasis, partial (2 cases); (4) emphysema, compensatory and partial (4 cases). These four different conditions were found in varying degree and association in 9 of the 12 cases examined, yet it is well known that all these appearances are common in the lungs of those dying slowly from profound toxic influences affecting the blood, the circulation or the central nervous system without reference to any specific pulmonary irritation whatever, and such would appear to be the fact in illuminating-gas poisoning.

The Brain. Of the 9 cases in which the brain was examined 6 presented marked congestion of the brain substance, pia and arachnoid; in 1 of these cases, however, there was evidence of a chronic meningitis; in the 3 remaining cases the brain and its membranes seemed normal. It would thus appear that cerebral congestion is a common result of poisoning from illuminating gas, occurring in the series of cases cited six times out of nine in which the brain was examined. To what extent this may be a cause of death is difficult to determine, but there can be little doubt that it is often a contributing factor, although not invariably present. In 3 of the cases there were marked changes in the corpus callosum, corpus striatum or ventricles, consisting of such conditions as softening, congestion and hemorrhages.

These appearances, which have also been reported by several other writers, are of the greatest interest. Some years ago Klebs pointed out the fact that carbonic oxid poisoning is capable of producing enormous distention of the cerebral arteries, and in

1893 Alexander Kolisko[1] referred to this distention of the central terminal branches of the anterior cerebral artery as the seat of thrombosis following distention and giving rise to the softening of the internal capsule, and especially of the lenticular nucleus which has been often observed. He states that he has seen several such cases resulting from CO poisoning, and refers to two more observed by Polchen. Another interesting case of softening of the internal capsule was reported by Broadbent[2] also in 1893. Schaeffer[3] has reported two fatal cases in which he found softening of the brain, cord and peripheral nerves. Von Sölder[4] reported the case of a man, aged forty-one years, who died four months after gas inhalation. At autopsy were found hyaline and fatty degeneration of the skeletal muscles, atrophy of peripheral nerves and degeneration of the anterior horns in the cervical and dorsal cord. J. W. Runeberg[5] reported two fatal cases with extensive softening in the lenticular nucleus.

SUMMARY. From the study of the foregoing cases the following conclusions regarding comatose cases of illuminating-gas poisoning may be drawn:

1. Leukocytosis is both high and persistent, rising in many cases above 18,000 and in a few fatal cases as high as 50,000. A differential leukocyte count shows preponderance of the polymorphonuclear cells. A high degree of leukocytosis is a very unfavorable prognostic symptom.

2. Elevation of temperature is observed in nearly all cases. The fever is usually moderate and of very irregular type. In many cases a subnormal temperature precedes the elevation, and it is often observed also in convalescence. The pulse is disproportionately rapid, as compared with the temperature.

3. The nervous symptoms are both varied and inconstant; convulsions occur in about 7 per cent. of all cases, and muscular rigidity in a slightly larger proportion.

The reflexes and pupil symptoms show great variability. The coma bears no definite relation to the intensity or duration of the fever. Coma lasting four or five days is not invariably fatal. In

[1] Wien. klin. Woch., 1893, Bd. vi., No. 11, p. 192.
[2] British Medical Journal, 1893, p. 1004.
[3] Deut. med. Woch., 1903, Bd. ii.
[4] Jahrb. f. Psychiatrie, 1902, Bd. xxii p. 287.
[5] Abhandl. der finnland. Gesellschaft. der Aerzte, Bd. xliv.

this series of 90 comatose cases only 17 cases, or 18.8 per cent., were fatal.

4. The results of combined phlebotomy and saline infusion justify the prompt and thorough employment of these measures.

5. Pneumonia is an infrequent complication, and in a large percentage of fatal cases the cause of death may be referred to cerebral lesions, such as congestion of the meninges and brain substance, hemorrhage of the cerebral capillaries, thromboses of small arteries or hemorrhage into and softening of the internal capsule and adjacent structures.

DISCUSSION.

DR. WEIR MITCHELL: It must be remembered that the gases used in different cities vary much in character. Has Dr. Thompson paid any attention to that?

DR. STENGEL: Several years ago one of my colleagues at the University of Pennsylvania made some experiments on the resuscitation of animals poisoned with coal-gas. The results were, briefly, that the animals that were severely poisoned by the gas could not be saved by venesection and saline transfusion, but fair results were obtained when defibrinated blood of the same animal was transfused. The observation Dr. Thompson referred to, that the poisoning is of the same character and the symptoms similar, whether the gas is taken in large doses and quickly or in small doses for many hours, shows that the firm combination of gas and hemoglobin is the important fact.

I have seen two cases, one in a boy at the Pennsylvania Hospital who recovered after a rather severe poisoning, the second a young woman, who inhaled the gas for several hours, had almost the same symptoms as the boy, but died. She lived in an out-of-the-way place, and I did not, I am sorry to say, advise the transfusion of defibrinated blood. I then recorded a mental note that hereafter I should insist upon such transfusion and not depend upon saline transfusion.

DR. PEABODY: One difficulty about the use of defibrinated blood, in my experience, has been that it is not always easy to get the blood when it is needed; and I regret to say that I have had a number of attempts made by surgeons who failed to get the blood into the circulation even when it was provided for them. I quite agree with Dr. Stengel that it is the proper thing to do.

DR. KINNICUTT: A considerable number of the cases reported by Dr. Thompson were studied by him in my service at the Presbyterian Hospital, and his observations would naturally correspond with my own. I wish, however, to

emphasize the point that neither the depth of the coma nor the duration of it can be considered a positive basis for prognosis. I have seen cases of coma of a fortnight's duration that entirely recovered.

I presume Dr. Thompson has mentioned in his paper an interesting and striking phenomenon in these cases, viz., the beautiful ruddy complexions of the patients, a coloring which persists in the fatal cases until death.

DR. HARE: In a research carried out in the University of Pennsylvania several years ago by Dr. Edward Martin and myself we came to conclusions quite different from those mentioned by Dr. Peabody. In regard to what Dr. Stengel has said I confess that the difficulties in the way of such a plan of treatment seem to be very great: not only to obtain the blood and see that there is no foreign body in it, as an embolus, but also because of the influences that may be feared from injecting the blood of one person into another. I confess also to being a little in the dark as to how the defibrinated blood possesses any great advantage over saline solution. I should not have supposed it contained a sufficient amount of hemoglobin to aid to any extent in the treatment.

DR. COHEN: We cannot speak of coal-gas or illuminating-gas poisoning without qualification. As Dr. Mitchell has pointed out, there are differences in the composition of illuminating gas in different cities, and probably differences at different times in the same city. Dr. Thompson has spoken of carbon monoxid as practically the only dangerous element, and no doubt it is the most dangerous, insomuch as it so changes the hemoglobin that the latter can with difficulty, if at all, take up oxygen again. So far as my reading goes, the use of defibrinated blood has failed to remedy this in human beings. But there are other elements in the coal-gas besides carbon monoxid; these are variable in quantity and kind, but chiefly they are hydrocarbons of the methane and other series. If one would take the trouble to read old Thomas Beddoes' book on *Factitious Airs* he would find recorded symptoms produced by experimental inhalation of what Beddoes and Watt termed "light hydrocarbonate" and "heavy hydrocarbonate" quite similar to some of those described by the reader. In the sum total of illuminating-gas effects we should, I think, allow for the hydrocarbon poisoning.

DR. KINNICUTT: May I add a word in regard to the use of oxygen. An extended experience in my hospital wards has shown it to be without any effect in these cases. The stability of the combination of the carbon monoxid with the hemoglobin would seem to preclude any benefit from its use.

DR. THOMPSON: Of course, the investigation of such a subject as this must be more or less unsatisfactory. I looked up the question of the composition of the gas, and found that it differs, as Dr. Mitchell and Dr. Cohen have said. It is impossible to determine always just what these patients have breathed,

but they all inhaled *something* that produced the symptoms that I have tried to analyze. In five or six cases that Dr. Kinnicutt and I saw water gas was used, which contains from 20 per cent. to 30 per cent. of carbon monoxid instead of from 8 per cent. to 10 per cent. as in the ordinary illuminating gas. As to whether carbon monoxid is the poisonous element, some recent experiments tend to prove that it is. It can be removed from the illuminating gas, and then the other constituents do not produce the same symptoms. Of course, my observations referred to the use of illuminating gas and not to coal gas proper as derived from stoves and furnaces.

In regard to the effect of the gas upon the hemoglobin, I did not mean to give the impression that that is not the great part of the difficulty in treatment. I did not have time to report all of this research, but I wish to say that much of the hemoglobin persists in many of the severe cases, and the blood is not saturated by the carbon monoxid, and yet some time after the blood is restored to a normal percentage of hemoglobin the patient may die. If the condition is solely due to a change in the hemoglobin the patient should always recover when the hemoglobin is restored to normal, but such is not the case. I have no experience with the use of defibrinated blood, for the reason that these cases must be treated promptly, and as we did not keep defibrinated blood on hand and did keep salt solution, we used that at once. In the majority of these cases bleeding and infusion gave good results.

IMMUNIZATION AGAINST RATTLESNAKE VENOM.

COMMUNICATED BY S. WEIR MITCHELL, M.D.

STATENS SERUM INSTITUT LABORATORIET,
COPENHAGEN, APRIL 27, 1904.

HON. DR. WEIR MITCHELL.

MY DEAR DOCTOR: I wish to thank you very cordially for your last letter. My answer I postponed until I should have gotten something which might be worth while of your reading.

Ever since I was sent hither by the Carnegie Institution to continue the investigation studies made by Prof. Flexner I have been immunizing a goat against the rattlesnake venom, in order to obtain an antidote against this particular venom. After five months from the start of immunization I have now succeeded in preparing a strong antivenomous serum, and I have the honor herewith to present you a portion of the same serum by this mail. As to the therapeutic value of this anticrotalic serum, I wish to inform you of my experiments on small animals.

0.0005 gram of the dried Crotalus venom is a sure killing dose for a guinea-pig weighing 250 grams when given intraperitoneally. (Death after twenty-four to thirty hours.) This dose is *one* dosis lethalis minimum. If we inject two minimal lethal doses the animal dies after three and one-half to four hours.

In the therapeutic experiments I have taken *twelve minimal lethal doses* to poison a guinea-pig, and my antivenomous serum was given at different intervals after the poisoning.

The result is as follows:

1. If the venom and antivenomous serum is injected simultaneously, 2.5 c.c. of the latter will protect a guinea-pig against 6 mg. (or twelve killing doses) of the dried Crotalus venom. No symptoms develop after the treatment.

2. If the antivenomous serum is given *one hour later* than the venom poisoning, about five times larger amount of the serum is

necessary to save the animal. Thus *two killing doses* (1 mg.) will be neutralized completely by giving *1 c.c.* of this serum one hour after the poisoning, while the control animal without the treatment will surely die after three and one-half to four hours.

To cure an animal, injected with the same amount of venom, after *two hours* from the poisoning it is necessary to give 2 c.c. of this serum.

Animals which are poisoned with the above-mentioned dose of venom become critically ill after three hours (if not treated with the antivenomous serum), and will succumb within thirty to sixty minutes later: but if *4 c.c.* of this antivenomous serum is given at this critical stage the animals recover rapidly, and no symptoms can be seen after two days. This experiment is extremely important in regard to the practical value of this antivenomous serum for the snake bites, because this proves that it is possible to subdue all critical symptoms by giving this antidote after such a long lapse of time from the accident.

The arrangement of the above therapeutic experiments is made in a manner to minimize the value of this antidote as much as possible, but in *practice* the venom will *never be absorbed so quickly*, as it is given *intraperitoneally* in this experiment, while the antidote can be injected into the vein in human cases.

Thus the practical value of this antidote will certainly be far greater than in the above-mentioned experimental cases.

I have also found that when the venom is given *subcutaneously* it is far less fatal to the animal than when given *intraperitoneally*. Thus a fatal dose of the subcutaneous injection is about ten times larger than that of the intraperitoneal injection. In the intraperitoneal poisoning 0.0005 will be 1 m., lethal dose, while in the case of the subcutaneous injection it takes 0.005 to kill a guinea-pig of the same weight.

I am now continuing this series of therapeutic experiments to study the poison immunity from different sides, under different conditions, on different kinds of animals.

I will at first ascertain the necessary amount of the antidote to save the animals poisoned *subcutaneously*.

For this purpose I am now working with rabbits, which are so

suitable to give the antidote *intravenously* and to poison *subcutaneously.*

I will leave the details to my next communication, which I will be able to write you before long.

I have sent a sample of this anticrotalic serum to the Carnegie Institution by this mail, also, with a brief remark on this preparation, and I hope it will satisfy the Executive Committee.

I wish to add a few lines here about the antidotal property of this serum. This antivenomous serum is effective against the rattlesnake venom *only.* It is prepared by using exclusively this particular venom. I am convinced of the falsehood of the bold claims made by Calmette, of France, who insists that the antivenin prepared by him through immunization of horses against cobra venom is active against all kinds of snake venom or scorpions. This broad claim is devoid of scientific grounds. Professor Flexner and myself have already pointed out the powerlessness of the Calmette antivenin against the other venoms, especially the rattlesnake venom.

Hoping this will find you in excellent health and thanking you for your kindness, I am

Your most humble servant,

HIDEYO NOGUCHI.

ABDOMINAL PAIN FROM UNSUSPECTED IRRITATION AT THE INTERNAL HERNIAL RING.

By CHARLES G. STOCKTON, M.D.,
OF BUFFALO.

This paper has to do with a cause of abdominal pain which, while it may not be unfamiliar to some, has nevertheless generally escaped description in literature, and appears to be overlooked by the profession. The importance of the subject rests not so much in the severity of the pain experienced, although this at times is great enough to induce semi-invalidism, but in the fact that it explains pain which might otherwise be attributed to graver visceral lesions and for the relief of which fruitless exploratory incisions might be undertaken. Some of my cases have been regarded as instances of chronic appendicitis, nephrolithiasis and questionable affections of the colon. In my experience the condition has always appeared in male adults, usually men of relatively active life. I have seen it in advanced age and in young men, but never in adolescence. The chief symptom complained of is pain generally referred to the lower quadrant of the abdomen, but occasionally appearing in the upper quadrants as well. Sometimes this pain is described as colicky in character, sometimes as a continuous misery, at other times as burning in character and suggesting irritation to the peritoneum. There is rarely localized tenderness, although it sometimes occurs. Occasionally there is a sense of abdominal uneasiness complained of, a vague unrest that seems difficult to describe; at times the patient speaks of moderate disturbance of the intestine as though occasioned by intestinal flatus, and one case suffered from severe gastric eructations. Generally these symptoms are relieved when the patient lies down; but this is not always the case, and some have experienced more pain when attempting rest than when actively engaged in exercise. As a rule exercise increases the distress, especially lifting or other efforts causing increased intra-

abdominal pressure. Several of my patients have been travelling men, who complained that they suffered when riding on the cars or in carrying in the hand sample-cases or other heavy articles. These disagreeable sensations are sometimes persistent, at other times intermittent in appearance. For instance, an individual may be free from the sensation for a month, and then there is a return for some weeks, and again an intermission. Like other abdominal troubles, it is likely to give rise to apprehension and nervousness on the part of the patient, and when the diagnosis is not made and the patient fails to experience relief from treatment he is likely to go from physician to physician. A number of my patients have been habitual drug-takers. The anatomic basis for these symptoms is to be found in a slightly overpatulous state of the internal hernial ring; not a condition so advanced as to admit of evident and easily recognized protrusion of the intestine or omentum, but one in which a slight bulging may be detected on palpation when the patient undergoes abdominal strain such as is produced by bearing down or coughing. The sensation communicated to the palpating finger is often quite unlike that of ordinary hernia. It is as though a very thin and almost inappreciable membrane presented at the opening in the inguinal canal, with a sensation of slight elasticity, as though a moderate gaseous pressure was operating behind it. I go into these apparently insignificant details of description for the reason that the condition is so easily overlooked, and in certain cases is difficult to recognize even when pointed out by one familiar with the condition. In some cases it would appear that the irritation is applied to the peritoneum alone; in others the small intestines would seem to be involved, but never have I seen in these patients those symptoms and signs which usually accompany ordinary inguinal hernia, and in only one of my cases has there ever occurred a recognized protrusion of the hernial sac. It is interesting to note that the symptoms above described occasionally occur in those having an inguinal canal so small that one would scarcely suspect it as being the source of trouble, many individuals having much more patulous inguinal rings without experiencing any inconvenience. The diagnosis, therefore, cannot rest on the mere question of the diameter of the internal ring, for the symptoms may arise in those in whom the ring is only moderately large, a condition of affairs that would not ordinarily be classed as abnormal.

In each of my cases perfect relief has been experienced by the

wearing of a sufficiently carefully adjusted truss. Some patients have worn this for years, and inform me that if the truss is left off the old symptoms reappear after a few days, sometimes almost immediately. In one very aggravated case, not reported in this series, seen in consultation with Dr. Charles Cary, who made the diagnosis, it was impossible to adjust a truss that would remain continuously in place, and for that reason it became necessary to resort to a surgical operation to lessen the caliber of the internal ring, after which procedure the symptoms were completely relieved.

I append the brief histories of 12 cases which represent only a proportion of those which have come under my observation during the past ten years. Perhaps I should apologize for presenting that which may appear to some as a trivial subject for discussion, and one which probably is known to others; but, as I have said, it is a condition sometimes causing great disturbance, although usually comparatively slight, is generally overlooked even by good men, and, finally, the discovery of this condition may occasionally save a man from undergoing a useless abdominal section.

This is one of my most interesting cases:

CASE I.—A. C. B., aged sixty-two years. The patient was rather stout, an active lawyer of New York City, a club man, highly intelligent, who subjected his symptoms to careful analysis. He complained most bitterly of disagreeable sensations in his abdomen. Many interviews and many pages of written accounts of his experiences were afforded me, but it remains impossible for me to fully understand what he attempted to explain. Among other things, he said he had a dull, aching pain during most of the time in various parts of the abdomen, accompanied sometimes by sharp twinges of pain, at other times by burning sensations. He also spoke feelingly of the distress accompanying intestinal peristalsis. He had a constant feeling of abdominal unrest. These sensations led to considerable mental uneasiness, so that he had consulted many physicians and tried various methods of cure initiated by himself. His symptoms were so vague that for a long time I failed to locate his difficulty and prescribed for him with little success at different times during a period of two years. Among other things, I recommended him to play golf, and while he found that this benefited his general health, it increased his abdominal suffering. This led to an examination of the inguinal regions, when I found a dilated right internal hernial ring, with slight bulging of what appeared to be the peritoneum. A truss was at once put on, and the patient left the city. Immediately thereafter some friend recommended to him the use of a nostrum. His symptoms completely disappeared. He felt certain that it was the effect of the nostrum. I felt equally certain that the relief followed the wearing of the truss. I could not persuade him to stop

the use of the nostrum and to try the truss alone. Matters proceeded in this way for over a year. Then he accidentally went without the truss for a short time, when the pain immediately recurred, although he took the nostrum constantly. After making some experiments on his own account, he wrote me that he was fully convinced that it was the truss and not the patent medicine which had relieved him. This is a somewhat remarkable case in the complete relief which has followed this simple measure in a man who had great intelligence and who was convinced against his will.

CASE II.—L. D. P., contractor, aged thirty years. Pain and discomfort of a vague character in both lower quadrants of the abdomen. He was in all other respects perfectly well. Found on both sides large internal rings; a truss was applied and relief obtained.

CASE III.—W. A. R., schoolteacher. Patient had long been constipated. For two years had suffered from abdominal pain and soreness, the first intimation of it having followed unusual efforts while carrying his sick wife. He is a powerful man, and, aside from the symptoms above narrated, was perfectly well. I found a patulous right inguinal canal and applied a truss, instructing him to keep his bowels open. The patient was relieved. Under date of March 14, 1904, he writes: "I followed your advice and found that the truss gave me relief as long as I continued to wear it, but it is necessary for me to wear it continuously."

CASE IV.—W. H. H., aged twenty-eight years, worker in the oil fields; suffered from typhoid fever nine months before, and since has had pain occasionally every two or three days, not always in the same part of the abdomen. A careful examination failed to discover anything wrong with him save the patulous inguinal canals, for which a double truss was applied. Relief was obtained at the time; but the subsequent history of the case I have not been able to follow.

CASE V.—E. L. H., aged thirty-eight years, bookkeeper; man of delicate frame and loose tissues. Complained of pain in various parts of the body, especially in the right side of the abdomen and back; he also suffered from frequent urination. He has a floating right kidney and patulous inguinal canals. A double truss was applied, with definite relief, but I have not been able to follow the subsequent history of the case.

CASE VI.—W. L. T., aged forty-five years, office-holder; had suffered from abdominal pain for the past twenty months without assignable cause. His pain was not located in any definite part of the abdomen, but was felt in various locations. It was always worse at night and left him on rising in the morning; he had been constipated for five years; both inguinal canals were patulous. suitable truss was fitted, and four years later he reported that he had been entirely free from pain since wearing the support.

CASE VII.—H. C. R., aged forty-eight years, lumberman; had suffered for a long time past from a very disquieting but inconstant pain in the left lower quadrant of the abdomen. He was well in all other respects. He had a large

hernial ring on the left side, and a proper truss was applied. Six weeks later he reported that he had been entirely free from pain since wearing the truss.

CASE VIII.—F. J. C., aged fifty years, accountant, standing at desk; had suffered for a long time with pain in both lower quadrants of the abdomen. There was considerable enlargement of the hernial rings, with slight though palpable bulging, but no definite hernia. A double truss was applied, following which there was complete relief.

CASE IX.—William G., aged thirty-five years, office work; had suffered from colicky pain in the abdomen for the past two years. His bowels are regular, digestion good; nothing could be found wrong with the man save that he has an overpatulous left inguinal canal with slight bulging. A truss was applied, and one year later he reported complete relief following the wearing of the truss.

CASE X.—W. R. F., aged thirty-one years, a storekeeper on docks. This patient had suffered for five or six years with noisy eructations of gas, which kept him awake at night. Of late he had been much worse. He also suffered from vague abdominal distress, poor capillary circulation, and a suggestion of hypochondriasis. He at one time had an inguinal hernia, which had been reduced. I immediately applied a truss, and this was followed by relief of his symptoms. Nothing else seemed to have any effect upon his gaseous eructations. Here it will be seen that the disturbance was of motor as well as of sensory character.

CASE XI.—W. W. B., aged sixty years, a travelling railroad inspector. He was well until three months ago, when he began to suffer from pain in the abdomen and a sensation of dragging or pressure in the inguinal regions, slow action of the bowels, eructation of gas, and a feeling of weakness or faintness in the epigastrium. The man was found to suffer from very marked chlorosis, having only 44 per cent. of hemoglobin, although the red blood count was between 4,000,000 and 5,000,000. There was found to be a right patulous internal ring. Treatment for chlorosis, while benefiting him generally, did not relieve the abdominal symptoms; so a truss was advised. He at once experienced relief, and wrote me, under date of March 9th, saying: "The truss worn relieved me to a large extent from pain and aches I had on the right side of my abdomen." He further said that his general health had not been improved by the remedies prescribed, and his chlorosis undoubtedly continues.

CASE XII.—A. W. H., aged forty-three years, a travelling man. Patient had never been sick; had been a travelling man for twenty-one years. Complained of lumbar and abdominal pains from the border of the ribs to each side, reaching down the flanks, not affecting the midabdominal regions. Careful examination revealed no reason for the pain, except an incomplete right inguinal hernia, for which a truss was applied and with relief. The subsequent history of the case I have not been able to follow.

A considerably larger number of cases might be reported, but this should be sufficient.

DISCUSSION.

DR. CARY: I have been very much interested in the substance of Dr. Stockton's paper. In order to have the case he referred to put on record I would like briefly to state it. The patient was my father-in-law, who had attained the ripe age of seventy-six years with good health. He discovered a slight hernia at the right inguinal ring, which I reduced easily, but it could not be held with the truss satisfactorily. He became a confirmed invalid because of the constant irritation, and during my absence from home on one occasion he was given opium to relieve the pain, and he soon became addicted to its use. Finally, although we could not feel the hernia, the irritation was so great that he could not bear the truss and had to submit to an operation. The mere trace of a sac was found and removed, and he was relieved of the pain and discomfort.

DR. PEABODY: I have one case exactly in line with these cases which I would like to put on record. The patient is a physician in my neighborhood who has frequently consulted me for very severe attacks of pain, without fever, located in the right lower half of the abdomen, which were ascribed by the physician who had been attending him to traction on a supposed adhesion from a supposed previous ulceration of typhoid fever. Other surgeons and physicians had seen him, and it was suspected that he had an appendicitis, but operation was not recommended because of his age and condition. This went on for three or four years, when the condition of things that Dr. Stockton describes was discovered, and the proof of the diagnosis is the same as in Dr. Stockton's cases, namely, that the application of a well-fitting truss has relieved him absolutely and permanently.

DR. BOND: I had a case which I took to be flatulency of the bowel on the left side and it gave me a great deal of distress for some time. He evidently had some disturbance of the intestinal tract, but on making an examination I found a slight protrusion at the ring, and putting on a truss relieved him entirely. I can recall having seen two or three cases of the kind.

DR. DOCK: I would like to relate a case that bears on this subject, and also on the interesting matter of abdominal pain felt at a distance from the lesion, as we see it sometimes in pneumonia. I was invited to a gall-bladder operation by a surgeon experienced in that line of work. The patient was a woman who had had several attacks of pain fairly characteristic of gallstone colic. Just before the day of operation a small, painful swelling appeared in the right inguinal region. This was operated upon first, when it appeared that there was a an incarcerated hernia at the internal ring, the mass involved not being larger than a small cherry, and the swelling due largely to edema in the surrounding

fat. On exploring the gall-bladder region no sign of old or new growth could be found, and no stone. Here it seems that the pain was caused by the small hernia, and it seems to me one can form a simple explanation of the pain, for the hernia itself would have been difficult to discover without some complication, as the inflammatory edema around the very small protrusion.

DR. STOCKTON: I feel convinced that in these cases there is not present a hernia in the ordinary meaning of that term. None of these cases have come to operation, and all have been relieved by truss except that which Dr. Cary described, in which case there had been a small hernia. The case was relieved by operation. I believe the condition is essentially one of irritation to the peritoneum.

ON THE MECHANISM OF EXOPHTHALMOS.

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AND

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We are still so far from comprehending the nature of exophthalmic goiter that light upon it from any side may be welcome. It has seemed probable that the study of the individual symptoms might be of value in this respect, and we have attempted to determine experimentally the mechanism of the exophthalmos. Since, however, it is after all impossible to be sure that the exophthalmos which one may produce experimentally is the same as that seen in this enigmatical disease, we have contented ourselves, for the time being, with the study of the phenomenon produced in animals by the stimulation of the cervical sympathetic, being well aware that although many surgeons hold that exophthalmic goiter is the expression of the continual stimulation of the cervical sympathetic, we are by no means possessed of conclusive proof that this is so.

It is hardly expedient to enter here into a discussion of the nature of all the varieties of exophthalmos. Those forms which result from hemorrhage into the orbit, from emphysema of the orbital tissues, from exostoses, tumors or cysts either in the orbit or in adjacent parts of the cranial cavity, from inflammation of the orbital tissues or neighboring tissues, etc., require no special explanation. Nor are we directly concerned with the various forms of pulsating exophthalmos due to arteriovenous communications, aneurysms, etc. In the absence of such definite and obvious causes there still remain to be explained a great many cases among which those associated with exophthalmic goiter are prominent. The greatest variety of explanations, sometimes resting upon experimental work, has been proposed, and these may perhaps be reviewed briefly.

These explanations rest either upon vascular alterations or muscular changes.

In especial favor is the idea that if from any cause the venous channels in the retrobulbar spaces become overfilled and dilated an adequate cause of exophthalmos is at hand. This is the basis of the explanation of those cases of pulsating exophthalmos in which arteriovenous communication exists as has been shown by anatomical investigation (Eales, Schlaefke). Similarly in those cases in which there is thrombosis of the cavernous sinus, there may be an extraordinary protrusion of the eyeball, and this is explained by Eales as due to pressure paralysis of the third, fourth, fifth, and sixth cranial nerves. In those cases, however, as was exemplified recently in the Johns Hopkins Hospital, the protrusion of the eye is associated with the most extreme œdema of all the tissues drained by the ophthalmic vein, so that it seems more probable that the exophthalmos is largely due to the œdematous swelling of the retrobulbar tissues, although in part directly to the enlargement of the veins.

It has been held by some authors that the widening of the retrobulbar veins, and hence the exophthalmos, is due to vasomotor paralysis (Sattler, Buschan, Matthiesen, Ferri), by others that it is due to active vasodilatation (Schmidt-Rimpler, Ehrlich, Rieger and von Förster). Still others ascribe it to the chronic passive congestion resulting from any compression of the veins or obstruction to the return of the blood to the heart. Diseases of the lungs, cervical tumors, bronchocele and the like (Nunneley, Taylor), intrabulbar hyperæmia (Eulenberg and Guttmann) and even œdema of the membrane of Descemet (Pauli) have been adduced as causes of the protrusion.

Most of these opinions are merely opinions and not based on any definite anatomical or physiological observations, but there has also been some experimental work along the same line.

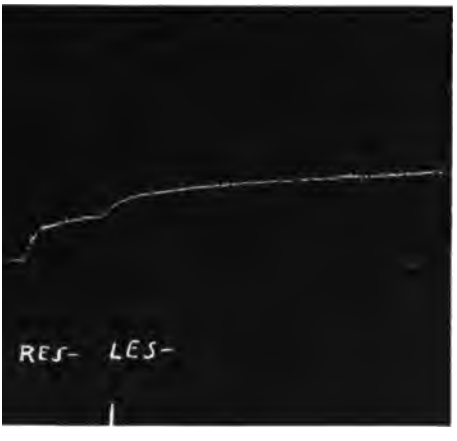
Boddaert, for example, experimented with rabbits, with the following results:

1. Section of the cervical sympathetic with ligature of the external jugular on the same side gave exophthalmos on that side lasting a few days.

2. Simple ligation of the external jugular gave only transitory results.

3. The first procedure plus section of the cervical sympathetic

E J, L E J. Right internal, right external and left external jugular.
the eye had returned nearly to its normal position.



of ligation of the veins.

CURVE 4.

All cervical arteries and veins ligated. Stimulation of the sympathetic still produces exophthalmos.

protrusion, which returns, however, to its maximum when they are again released. Finally the release of the external jugular veins allows the eye to sink back to its normal position. All of these phenomena occur, as may be seen in the curve, practically instantaneously. The absolute protrusion in one dog from which we obtained the curves which we reproduce here, when calculated in millimeters, was 3.2 mm. (See Curves 1 and 2.)

From this experiment it will be seen that the degree of protrusion produced thus by suddenly clamping the jugular veins is considerable, but would doubtless yield after a time to the establishment of a collateral channel of outflow for the blood. If the jugular be left ligated, however, a great œdema of the face and eyelids associates itself with the distention of the veins and only gradually disappears. This œdema, which apparently involves also the retrobulbar tissue, seems to aid greatly in the protrusion of the eye, and we have thought it an important factor in those cases in which the cavernous sinuses are thrombosed.

Now it is well known that without any mechanical interference with the circulation of the neck and head one may, by stimulating the cervical sympathetic nerves by means of a current from an induction coil, produce a great exophthalmos (Curve 3). Associated with this protrusion there is a retraction of the eyelids and a maximal dilatation of the pupils. Whether there is any alteration in the size of the vessels about the eye and in the retrobulbar space we could not determine by inspection, but our impression was that there was no definite change. Dr. Randolph was kind enough to observe the retina of these dogs with the ophthalmoscope while the sympathetic trunk was being stimulated, but could not make out any alteration in the size of the retinal vessels.

Nevertheless the idea that this exophthalmos is due to the distention of the retrobulbar vessels is so deeply rooted that other experiments were made to control these results.

In one dog both carotids were tied and the cervical sympathetic stimulated. Quite the same curve was produced as in the dog with the intact vessels. In another dog both common carotids, both vertebral arteries, and the jugular veins were tied (Curve 4). A slight protrusion resulted from the ligation of the veins, which was first performed, but after that the stimulation of the cervical sympathetic trunk produced such a great additional protrusion that there seemed no doubt that its action was independent of the circulation.

Finally a dog's head was completely severed from the body and allowed to drain of its blood. Stimulation of the sympathetic now produced exophthalmos quite as marked as in any of the other dogs.

We conclude, therefore, that that form of protrusion of the eyeball which results from stimulation of the cervical sympathetic is entirely independent of the changes in the blood supply. What, then, we may ask, is the mechanism of the process?

Numerous theories as to the action of the muscles have been put forward to explain the protrusion. On the one hand relaxation of the eye muscles and other supports of the eye (Cooper), fatty degeneration and atony of the eye muscles (Traube, Recklinghausen, Bristowe), toxic atony of eye muscles (Lemke), have been held accountable. Fürst, however, quotes a case of ophthalmoplegia to prove that, contrary to Lemke's statement, weakening of the eye muscles produces, if anything, enophthalmos. On the other hand, spastic conditions of the eye muscles (Brücke), overaction of the oblique muscles where the recti are paralyzed (Salomonsohn), have been thought to produce the same effect.

Finally, Sappey, Wagner and others have thought the protrusion due to the contraction of the so-called musculus orbitalis of Müller. Müller in 1859 described the smooth muscle of the eyelids and also this cone of smooth muscle and elastic and fibrous tissue which surrounds the eye and by its contraction keeps it forward. Wagner, who attempted in vain to produce exophthalmos in the head of a decapitated woman by stimulating the sympathetic, does not think that the muscle is sufficiently developed in man to have such an action. Th. Harling described in detail the antagonistic action of the muscle to that of the voluntary muscle of the eye; from its funnel shape and its anterior attachments it keeps the eyeball pressed forward. Since, as Müller stated, it is innervated by the cervical sympathetic, the explanation of the exophthalmos may be reached in a simple way. In man, however, he thinks its function chiefly protective. Sappey in 1868 reported a dissection showing that in man the protrusion of the eyeball after stimulation of the cervical sympathetic is due to the existence of smooth muscle fibers which form part of the orbital aponeurosis which constitutes a true fibromuscular sheath. The muscle forms a contractile cuff of conical form, the apex being posterior, so that by its contraction the eye is pressed forward.

We have studied this structure in man and in the dog and find

that, as these authors state, it is far better developed in the dog, where it forms a smooth conical mantle about the eye, continuous anteriorly with the musculature of the lids and forming abundant attachments about the margin of the orbit, passing backward thence, to end about the foramen through which the optic nerve enters the orbit. Nevertheless, this muscular tissue is by no means wanting in man. Here, too, it is continuous with the smooth muscle of the eyelids, and is continued backward in the membrane which lies immediately outside of the bulb (capsule of Tenon).

Anatomically everything seems, therefore, to point to the possibility that protrusion of the eye might be produced by the contraction of such a muscle.

We have also endeavored to ascertain the extent of the participation of this smooth muscle cone in the production of exophthalmos by direct observation. The top and side of the orbit were removed in a dog and the bulb thus laid bare and freed from surrounding fat. The cervical sympathetic was then stimulated, and we could see a distinct peristaltic wave pass backward throughout the length of this cone, pressing the eyeball forward into the position seen in exophthalmos. Allowing the muscle a few minutes for rest this could be repeated several times. We then cut with scissors around the middle of this membrane-like cone so as to completely sever the anterior from the posterior half. Stimulation now produced a contraction of the posterior or small end of the cone, which retracted out of sight into the optic foramen while the eyeball remained stationary.

The simple conclusion for these experiments seems to be that on stimulating the cervical sympathetic nerve the ocular protrusion which results is due not to vascular changes but to the peristaltic contraction of the cone of the musculus orbitalis which presses the eye forward.

We have, through the courtesy of the surgical staff of the Johns Hopkins Hospital, been able to observe two cases in which, in human beings, stimulation of the cervical sympathetic trunk just below the superior cervical ganglion was carried out. In neither was there any visible exophthalmos, although in both the pupils became greatly dilated on that side. Jonnesco reports, however, the production of exophthalmos in human beings by the use of a strong current in stimulating the sympathetic.[1]

[1] XIII. Cong. Internat. de Méd., Paris, 1900.

We were further interested to determine whether or not we might produce exophthalmos without pupillary dilatation by stimulating some other part of the sympathetic system. In other words, whether we might find some point at which stimulation would not produce both these phenomena. We therefore traced the sympathetic cord back into the thorax in a cat under artificial respiration, and found that the requisite impulses were produced along a path which could be traced into the second ramus communicans, *i. e.*, into the second ventral root in the dorsal region; but here stimulation produced both exophthalmos and pupillary dilatation, and in spite of the most painstaking exploration of the dorsal and cervical cord, the floor of the fourth ventricle and the aqueduct, we were unable to find the point we searched for, nor even to produce either of these phenomena from these higher centers. Further search, however, may reveal such a point. Similarly our efforts to produce exophthalmos by stimulating nerves going to or from the thyroid were futile.

In view of the objection which has been raised to the idea that continual stimulation of the sympathetic might form the basis of the exophthalmos in Basedow's disease, we kept up a mild stimulation of the sympathetic in dogs for periods of eight and ten hours, and found that the exophthalmos persisted fairly well all day. A gradually if slightly increasing stimulus seemed, however, to be necessary to maintain the degree of protrusion obtained at first.

We may conclude then that—

1. Obstruction to the outflow of blood from the veins of the orbit produces at once exophthalmos, which is relieved by the establishment of a collateral circulation. This process, however, is completed so slowly that in the mean time the orbital tissues as well as the tissue of the face become very œdematous, thus adding to the exophthalmos.

2. Entirely independent of any circulatory changes is the exophthalmos produced directly by the stimulation of the cervical sympathetic nerve. This protrusion is due to the peristaltic contraction of the orbital muscle.

From these experiments we can draw no certain conclusions as to the mechanism of the exophthalmos in Graves' disease, but the possibilities are perhaps more closely defined.

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A NEW CASE OF CHLOROMA WITH LEUKEMIA.

WITH A STUDY OF CASES REPORTED SINCE 1893.

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AND

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INTRODUCTORY AND CLINICAL STUDY, BY DR. DOCK.

In 1893[1] I reported a case of chloroma with an analysis of the cases then known. Including my own case there were only seventeen, but I felt justified in giving a clinical picture of the disease, and in assigning it an anatomical basis. The chief clinical features were: "The appearance, usually before the age of twenty, of anemia without evident cause, with loss of strength, dyspnea and emaciation; hemorrhages in skin, mucous membranes (epistaxis), or internal organs (retina); rapid pulse; ocular symptoms, such as difficulty of vision, strabismus and especially exophthalmos, without the special features of Basedow's disease and with tumor in the orbit; deafness and ringing in the ears and tumors in the temporal regions, or in the cranium in other parts, or in other parts of the body." Besides the resemblance of the symptom-picture to that of many cases of leukemia, especially acute leukemia, three out of nine cases of chloroma, observed since leukemia was known, showed "an increase of the leukocytes, two of them an increase such as is seen usually only in leukemia." At that time leukemia was not so well known as it is now, and I felt obliged to devote considerable space to a consideration of the histology of the blood. I also discussed the position of the anatomic change in chloroma and concluded that it might

[1] Chloroma and its Relation to Leukemia, American Journal of the Medical Sciences, August, 1893.

better be termed lymphoma (in the sense originally used by Virchow, who gave leukemia as the first example of the lymphomatous disease) than sarcoma, lymphosarcoma or lymphadenoma. An interesting feature of the morbid anatomy of chloroma was shown by my analysis, as it had been by some earlier writers—the "predilection of the periosteum, especially that of the head, but also fibrous tissue in general."

This article served to call attention anew to the subject. Since then more than twenty cases have been reported, some of them with elaborate studies, though without demonstrating any essential changes in the clinical and anatomic conceptions of the disease. Recently I was fortunate enough to have another case. Like many others it could not be investigated as thoroughly as it deserved, but I have thought it might well serve as the basis of an analysis of the cases reported since my former paper was published. The anatomic study of the case has been made by my friend and colleague, Dr. A. S. Warthin, whose investigations in the anatomy and pathology of the blood-forming organs have already been so valuable.

CLINICAL SUMMARY OF THE CASE. *Weakness, anemia, headache, tinnitus, deafness, of one year's duration; loose teeth; emaciation; leukemic changes in blood; death from asthenia.*

L. J., aged forty-five years, farmer, Swede, admitted to the Medical Clinic, Hospital of the University of Michigan, December 1, 1903, on account of weakness and anemia.

His father died at sixty-one years of age, from an acute illness; his mother died at eighty-two, of a disease characterized by difficult breathing. Patient has been married twice; has had two healthy children by each marriage.

Patient was strong as a child. He had measles at six years; since then has never required a physician until the present illness. Denies venereal diseases.

Was a farmer in early life; then worked in the woods and in lumber mills from 1883 to 1891; then resumed farming. He formerly used alcohol in excess; has taken none in the last year, and has also given up tobacco in the last year.

The present disease began in November, 1902, with a feeling of fatigue and dyspnea on exertion. Treatment was without benefit. For six weeks the patient was confined to bed by weakness; "his pulse could hardly be felt." In the early part of the disease he complained of pain in the left side of the head. Hearing was gradually lost, while a pounding noise, like that of a railroad train, was present. Also in the early stage the teeth became loose, without salivation or other local symptom. A change in the color of the skin was noted in the very beginning. There has been a gradual loss of weight, amounting now to twenty-five pounds. The appetite is fairly good; bowels constipated. The patient

sleeps well. He complains of dyspnea only on exertion, but says he is very weak.

Status Præsens. December 2, 1903. Man of large frame; muscles small and soft; panniculus thin. In the right axilla are three enlarged glands, the largest the size of a white bean; no other superficial glands enlarged.

The expression is weary and apathetic. Deafness and seeming lack of intelligence render the examination difficult.

The face is pale and sallow; the skin over the body very pale, but not sallow; over the legs and arms sallow. On the abdomen, just below the right costal margin, is a pale brownish pigmentation. There is a dark-brown line in the skin extending from the tip of the ensiform to the pubes, and an irregular brownish patch in the right lumbar region, but no pigmentation in other parts of the body. The skin in general is smooth, dry and elastic. Over the right shoulder is a mass the size of a large orange, firm, elastic, movable under the skin, but fixed below. A smaller, softer, bilobed mass occupies a similar position on the left shoulder (lipomata?). There is no edema.

The skull shows no abnormality except two scars on the left malar and left frontal regions, respectively, from injuries. The scleræ are very pale; pupils equal and react well. The lips are pale; there is marked *fetor ex ore;* tongue dry, pale, with thin gray coat, fissured and marked by teeth. The teeth are worn, but only a few are missing. The gums are red, slightly swollen, their edges covered with a grayish-green deposit extending from the teeth, removable by rubbing. Pharynx negative.

Auscultation and percussion of lungs negative. Apex beat in the fifth intercostal space, nipple line. Dulness not enlarged. Sounds are clear, except the first in the pulmonary area, which is replaced by a long, loud, blowing murmur.

Radial artery not thick or tortuous. Pulse of moderate size, quick. Blood pressure (Riva-Rocci) 133 mm.

The abdomen is below the level of the ribs; inspection and palpation negative. The spleen cannot be felt.

Urine. No albumin or sugar; few leukocytes; many cylindroids. Owing to the patient's lack of intelligence and his unexpected death the urine examination was not complete. Albumose tests not made.

Blood. Pale and watery; fresh drop shows few red cells, varying in size and shape; leukocytes increased. Red blood corpuscles 509,600, leukocytes 35,669, hemoglobin 15 per cent. For differential count see below.

December 4th. Patient fainted while being taken to closet, and vomited coffee and milk taken a short time before. Examination just after this showed the murmur louder and more widely transmitted; the aortic second sound weak; pulse of moderate volume.

In the clinic the patient complained of rather marked pain on pressure over the sternum and tibiæ.

At 5 P.M. again vomited food soon after eating it; complained of headache; temperature, 99.4° to 102°; pulse, 94 to 104; respirations, 18 to 26.

5th. Examination of stool (Dr. Dock); large and formed; good digestion; no blood, pus, or mucus; no protozoa or ova.

Test-breakfast withdrawn in fifty-five minutes, 25 c.c., sour odor, light yellow, with a small blood clot; excess of mucus. No acids, no peptic digestion (Mett). Microscopic examination: starch, few red blood cells.

Ophthalmoscopic examination (Dr. Carrow): Numerous hemorrhages in both retinæ; vision much impaired.

5 P.M. Complains of headache and nausea; refuses to take food. Strychnin hypodermically. Temperature, 99.4° to 102.5°; pulse, 96 to 108; respirations, 20 to 26.

6th. Test-breakfast, forty-five minutes; 15 c.c.; excess of mucus, blood stains. No acid; no pepsin. Microscopic examination negative.

5 P.M. Patient is nauseated and refuses to eat. Became restless later. Temperature, 99.2° to 100.2°; pulse, 94 to 112; respirations, 20 to 26.

7th. Patient slept fairly well. Boas' breakfast, one hour; 15 c.c.; sour odor, neutral reaction; trace of peptic digestion. Microscopic examination negative.

5 P.M. The patient is very weak, with small and frequent pulse (120). Temperature, 98° to 100.4°; pulse, 106 to 120; respirations, 24 to 36.

8th. Was very restless in the night. Six A.M. Temperature, 98.1°; pulse, 104; respiration, 28; skin cold. Talks irrationally; refuses all nourishment. 8 A.M. Temperature, 96°; pulse, 100; respirations, 32.

Subcutaneous injection of physiologic salt solution at 10.37 to 10.50 A.M., 12 ounces. Riva-Rocci 108 at beginning, 100 at end. Pulse weaker. Died 11.28 A.M.

EXAMINATION OF THE BLOOD. DIFFERENTIAL COUNTS.

Date.	Red blood cells.	Leukocytes.	Hemoglobin.	Normoblasts.	Megaloblasts, degenerated.	Free nuclei.	Small lymphocytes.	Large lymphocytes.	Lymphocytes, marrow.	Polynuclear.	Eosinophile, polynuclear.	Eosinophile, mononuclear.	Myelocytes.	Transition and mononuclear.	Basophile.
December 3 . . .	509,600	35,669	15	.....	1	.....	6.7	3.9	79.9	7.4	0.8	.....	0.4		
" 4 . . .	.....	.....	.....	.....	.....	1.8	6.9	5.3	79.6	5.7	0.8	0.1	0.2		
" 6 . . .	.....	.....	.....	1	.....	.....	5.8	5.0	82.6	5.6	0.2	.....	0.1	0.5	
" 8 . . .	820,000	.....	15	1	.....	.....	2.5	2.3	81.6	7.4	2.0	0.2	1.9	1.3	0.4

The blood was stained with hematoxylin and eosin, Ehrlich's triacid and Wright's stains. The counts given are all taken from Wright's stains, which

correspond closely to the hematoxylin and eosin counts. The triacid was used only to confirm the neutrophile myelocytes.

The blood shows very few nucleated red cells, almost all normoblasts. The only megaloblasts found have degenerated nuclei.

In all the preparations of one day, December 4th, there are many "free nuclei," up to 18 per 1000 leukocytes. At other times these are too few to count. They are very small, stain intensely and show no protoplasm.

The small lymphocytes are usually typical, but some of them show slight fragmentation of the nucleus.

There is a small proportion of typical large lymphocytes, some of which also show fragmentation of the nucleus. These two groups together are only slightly increased above normal.

From 79.6 to 82.6 per cent. of all the leukocytes differ from typical lymphocytes, but resemble these cells in certain respects, and differ still more from other normal leukocytes. They resemble closely the undifferentiated lymphocytes of the bone-marrow, and for convenience I class them in the table "marrow lymphocytes." They range from the diameter of a red blood corpuscle to two or more times that size. They are often oval or even broadly spindle shaped. Many of them have no visible protoplasm. Others show a narrow, crescentic or annular rim, and still others a wider protoplasm up to an amount usual in large mononuclear cells of normal blood. In most cells of this class the nucleus is round or oval, almost or quite filling the cell. In some the nuclei are reniform, or more or less incised on one side, or sometimes bilobed. Sometimes the two lobes partly overlap; sometimes they are partly or quite separated. When there are two nuclei these are sometimes unequal. The nuclei stain moderately well with hematoxylin and methylene blue; faintly with triacid. They look unevenly blurred in many cases, but in general stain like the nuclei of large lymphocytes, and marked failure to take the stain and other evidences of degeneration, so often seen in leukemic blood, are unusual. The protoplasm usually takes a blue with Wright's stain, sometimes darker than the nucleus, without granulation, but often with a spongy or reticulated appearance. Triacid stains it a pale pink or not at all. Eosin can be almost entirely washed out, but sometimes leaves a pale pink, and in some cells stained with hematoxylin and eosin the protoplasm of these cells has a pale-blue tint. The protoplasm is sometimes ragged at the edges; sometimes there are few or many knob-like processes on the edges, stained a pale blue, and having a smooth, homogeneous appearance.

These cells cannot be separated readily from those classed large mononuclear, so far as general appearance is concerned. The distinction here is based upon the different appearance of the protoplasm and the relatively smaller and more distinct nuclei in the large mononuclears. While those classed as marrow lymphocytes, as well as the large mononuclears, have no granulations in the protoplasms, there are a few cells having the general shape and proportions of

large mononuclears that show a few eosinophile granulations, sometimes very small ones, scattered over a pale and sometimes vacuolated protoplasm.

The polynuclear cells vary much in size, nuclear structure and protoplasm, resembling in their polymorphism the polynuclears of mixed-celled leukemia. In size they vary from one to four times the diameter of a red blood cell. The nucleus is sometimes in separate parts, especially in the larger cells. The nuclei stain deeply as a rule, but the large ones show a reticulated structure with thickening at the nodal points. The protoplasm shows, with proper stains, a fine, or in rare cases somewhat coarse, acidophile or neutrophile granulation. A few of the smaller cells of this group are probably Ehrlich's pseudolymphocytes.

The polynuclear eosinophiles, relatively rather low, but absolutely within normal limits, show no marked abnormalities in size or structure. Many have nuclei less polymorphous than in normal blood, but still within the range of variation in such cells in general.

Mononuclear eosinophiles were present only two days out of four in small proportion. Most of them are large, but some are about the size of red blood corpuscles. In some the protoplasm is very narrow. I have counted among the eosinophile cells some that have very few granules, as mentioned above. In one cell, not included in any of the counts, a "marrow lymphocyte" without protoplasm, there were ten large eosinophile granules scattered over the cell without any explanation by way of artefact.

The myelocytes (neutrophile) vary in the usual manner from small to large. Some of them have vacuoles in the protoplasm.

Basophiles appeared only on the last day. They all have round or elliptic, eccentric nuclei. Some are small, some large.

The red blood corpuscles show slight changes aside from their very scanty number. The cells vary somewhat in size, but marked departures in size and shape are not present. The cells take the usual stains well; they show very little polychromatophilia. Normoblasts are few. No typical megaloblasts are to be found, but some of the large nucleated red corpuscles have trefoil or irregular nuclei.

During the patient's life-time the full details of the blood were not known, but I had carried the examinations far enough to show that while the blood resembled in general that in many cases of acute leukemia it had some important differences in the details of the cells as well as in the differential count. It was more polymorphous than is usual in acute lymphocythemia, and resembled somewhat closely the blood of a case of acute lymphocythemia with extensive intestinal lesions that I had studied a short time before, and a report of which will be made by Dr. Warthin at this meeting.

The diagnosis, as made at a clinical conference December 4th, was: acute leukemia, possibly lymphocythemia, in the late stage of a severe anemia of unknown cause. The points of resemblance, and of difference as compared with pernicious anemia with late lymphocytosis, were brought out. Chloroma did

not then seem as probable as acute lymphocythemia with lesions in the alimentary tract, but before the autopsy on account of the absence of distinct gastrointestinal symptoms while under observation, I thought chloroma was more probable, notwithstanding the absence of the peculiar head symptoms.

Permission to make an autopsy was obtained with great difficulty and after much loss of time. It was impossible to examine the head, and owing to lack of time the examination of the other bones was seriously limited.

Autopsy protocol, December 9, 1903, 10 A.M. (Dr. Warthin.) Body well built. No deformities or anomalies. Length 160 cm. Abdomen on level of ribs. Left side of thorax not as full as right. Musculature fair; muscles in fair condition. Rigor mortis marked, present throughout. Panniculus moderate. Slight edema over ankles. Body heat entirely absent. No signs of decomposition.

Skin is very pale on the whole. There is pale-red hypostasis over the back. The flexor surfaces of both upper and lower extremities show no unusual pigmentation. Over the upper portion of the right thigh there is an area about the size of a hand showing scattered spots of pale-brown pigmentation. In the median line of the abdomen there is a pale linea fusca. The wrists and back of hands are tanned. Over the inner side of the right elbow there is a small ecchymosis, and numerous small petechial hemorrhages are scattered over the flexor surfaces of both upper and lower extremities, being most marked over the left arm and less numerous over the lower extremities. Transfusion mark in right pectoral region. The hair is thin over the vertex, and harsh and dry. The beard is slightly gray. The teeth are in fair condition.

Over the outer third of the left clavicle there is a subcutaneous tumor 7 cm. long by 5 cm. wide. It is slightly lobulated and at its lower pole there is a smaller mass 2 cm. in diameter. The tumor is freely movable, is not adherent to the skin, is semielastic. Over the outer third of the right clavicle there is a similar roundish tumor 7 cm. long by 6 cm. wide. It is firmer in consistency and is less freely movable than the growth on the left. It is not adherent to the skin and does not seem to be attached to the periosteum. It does not move with the arm. Both tumors present the characteristics of lipomata.

The axillary glands are palpable, but not enlarged. Cervical glands not enlarged. The inguinal glands are just palpable, not enlarged.

The head was not opened. (No permission.)

On section the muscles are pale brownish-red; panniculus a pale lemon-yellow.

The diaphragm is at the fourth intercostal space on the right, and at the fifth rib on the left. The first costal cartilages are ossified.

On removing the sternum its inner surface is found to be covered with a dense infiltration about 1 cm. thick and having a distinct light grass-green color. The infiltration is most marked over the upper part of the sternum, and here the color is more decidedly greenish. The sternum is softer and more friable than normal, and is easily fractured or cut. The sternal marrow is hyperplastic, pyoid in character and has a slight greenish tinge. Exposure to the air and slight drying

caused the green color of both the infiltration and marrow to become more marked.

The mediastinal fat is of fair amount, and of a pale lemon-yellow color. Contains a few small, pale lymph nodes. In the thymus fat there are several large lymphoid structures, one of which is about the size of an English walnut and has a greenish-gray color. On section it is very edematous, medullary in consistency, greenish-gray and showing fine lines of anthracosis. The other lymphoid structures in this region are soft, grayish, edematous and more or less anthracosed.

The apex of the heart lies in the fifth intercostal space half-way between the left parasternal and nipple lines. The heart extends four finger-breadths to the right of the median line. No fluid in either pleural sac.

The pericardium is distended. Contains 40 c.c. of clear fluid, the increased intrapericardial tension being due to dilatation of the heart.

The heart is much enlarged, the enlargement being due chiefly to dilatation of the auricles. Weighs about 700 grams. On the anterior wall of the right ventricle there is a large, triangular, tendinous spot measuring 5 x 5 x 4 cm. Near the apex of the left ventricle there is a smaller one measuring 2 x 1 cm. Smaller ones on the posterior wall of the right ventricle. The subepicardial fat is increased in amount and is of a pale lemon-yellow color, translucent and edematous. Everywhere over the surface of the heart along the course of the smaller vessels there are great numbers of small, punctate hemorrhages. They are most numerous on the posterior wall near the apex. Coronary veins greatly distended. The auricles contain a pale plum-colored blood and large white clots. The walls of both ventricles are lined by similar white clots. The mitral and tricuspid orifices are dilated. The heart muscle is pale and soft.

The left lung weighs 1000 grams and measures 28 x 18 x 6. Pleura adherent posteriorly and over base by old and rather tough adhesions. The lung is voluminous, pale grayish-pink above, and moderately hypostatic posteriorly. On section it is very edematous, yielding an abundant foamy exudate on slight pressure. Very small, whitish, airless areas throughout. Anthracosis moderate.

The right lung weighs 1120 grams and measures 30 x 18 x 6. Adherent posteriorly and over the base by very firm adhesions. Pleura covered with the remains of old adhesions. Lung very voluminous. Color similar to that of left lung. Consistency somewhat more firm than that of left lung and the cut surface is darker in color, otherwise similar. The small, whitish, airless areas are more numerous in lower lobe.

The pulmonary veins contain large pale clots. The mucosa of the larger bronchi is pale, that of the smaller is injected. The smaller bronchi are somewhat dilated. The bronchial glands are enlarged, very pale gray, soft and edematous. Thoracic duct negative. Thoracic and cervical esophagus negative.

No pathologic changes in mouth and throat so far as could be ascertained

(section not permitted). Neck organs examined from below. No pathologic changes found.

No fluid in the peritoneal cavity. The omentum is rolled up; moderately rich in fat of a very pale-yellow color. The lower border of the stomach extends one finger-breadth below the umbilicus. The lower edge of the liver in the median line is four finger-breadths below the ensiform and one finger-breadth below the edge of the ribs in the right nipple line. The pylorus is four finger-breadths to the right of the median line. The colon is contracted, filled with hard fecal masses. The duodenum is moderately dilated; the remaining portion of the small intestine is collapsed. The appendix is very long and large, the distal one-third dilated. The greater part of the appendix lies in the pelvis and is attached to the sigmoid flexure by recent adhesions, which are very vascular. The peritoneum about the appendix is thickened. No evidences of any perforation, old or recent.

The spleen weighs 426 grams and measures 17 x 11½ x 5 cm. It is rather soft and flattens on pressure. The capsule is slightly thickened and over it there are scattered small hyaline tags. There are four distinct notches on the anterior border. On section the pulp is pale red, soft, swells up above the stroma and is easily scraped away. The stroma is covered up by the hyperplastic pulp. The follicles are very few and small and can be seen only in a few places near the capsule. The cut surface presents a moderately shagreened appearance and is of a uniform pale red.

The left adrenal is very small, completely surrounded by pale-yellow fat. On section it shows no change. The right adrenal is likewise very small and embedded in a thick capsule of pale fat. On section shows postmortem change of the medulla, otherwise negative.

The left kidney has a very thick fatty capsule of a pale lemon-yellow. The fibrous capsule is stripped with some difficulty. The organ freed from its capsules weighs 190 grams and measures 14 x 6½ x 3½ cm. The cortical surface is very pale and slightly granular. Traces of the fetal lobulations are present. The cut surface is very pale and cloudy. The outlines between the labyrinths and medullary rays are not distinct. The consistency is somewhat diminished. The pelvis presents no pathologic changes. The subpelvic fat is very abundant.

The fat and fibrous capsules of the right kidney are similar to those of the left. The stripped kidney weighs 190 grams and measures 17½ x 7 x 3 cm. The organ contains more blood than the left, the outlines between the medullary rays and the labyrinths being more distinct. Scattered over the cortical surface are small, slightly elevated, pale-yellow or grayish spots about 2 mm. in diameter. On section these spots are nearly round and are located for the greater part just beneath the cortical surface. They are fairly firm and are not affected by pressure. When scraped with the point of the knife they yield an abundance of cells. In other respects the appearances resemble those seen in the left kidney.

The ureters are dilated and filled with slightly turbid urine. The bladder is

greatly distended and filled with slightly turbid urine. Its wall is thin, and the mucosa very pale. No other changes.

(The stomach was ligatured at the cardiac orifice and removed in connection with the intestines, which were ligatured at the rectum. The contents were preserved for chemical examination.) The stomach is dilated, its wall thin, and the mucosa very pale. Lymphoid follicles prominent. In the submucosa of the fundus there is a small round tumor about the size of a pigeon's egg. The mucosa is intact over the growth, which has a firm consistency.

The intestines are very pale. The lymphoid structures are rather prominent, but not distinctly enlarged.

The liver weighs 2230 grams; its greatest measurements are 29 x 20 x 11 cm. The general color of the organ is a light yellowish-brown. Over the surface and just beneath the capsule there are many small yellowish or whitish spots. On section these spots extend a short distance into the liver substance, so that they appear as round or oval areas about 2 to 4 mm. in diameter. They are sharply circumscribed, fairly firm, but yield an abundance of cells on scraping with the point of the knife. Besides these small spots there are seen underneath the capsule larger pale areas, less sharply circumscribed and of a more reddish-yellow color. On section these areas also extend into the liver and appear to be made up of groups of liver lobules that have suffered some parenchymatous change. On the main section a narrow strip of liver lobules showing characteristic nutmeg appearance is found just beneath the capsule. The remaining portion of the organ is very anemic, the central veins empty and the lobules small and of a light chocolate color. Similar small yellowish areas to those seen underneath the capsule are scattered over the surface.

The gall-bladder is adherent to the omentum. It is moderately filled with dark greenish-brown bile. No stones or sand. Bile passages patent. Examination of portal vein is negative.

The pancreas is about normal size, very pale and somewhat softer than normal. Section negative.

The mesenteric lymph glands are slightly enlarged, pale and soft. The lymph glands of the portal fissure are very large, pale, soft and homogeneous on section. The retroperitoneal glands are moderately enlarged, very pale and of medullary consistency. The hemolymph nodes are pale, but present no other gross changes. No greenish color seen in any of the abdominal or retroperitoneal lymph glands.

The examination of the sexual organs, internal and external, is entirely negative.

On stripping back the prevertebral tissues the bodies of the vertebræ are found to be covered with flattened greenish masses varying from 4 to 10 mm. in thickness. Over the intervertebral disks the greenish color barely shows, so that the greenish vertebræ are sharply outlined from each other by the whitish disks. In the lumbar region the color is most marked over the bodies, but in the thoracic

region the greenish tissue is more marked along the sides of the vertebræ. The greenish tissue extends for a short distance over the ribs. It also infiltrates to some extent the prevertebral fat-tissue. A thin layer of the greenish tissue is found in both iliac fossæ and over the inner side of the sacrum. It is not present on the clavicles or on the long bones of the lower extremities. The bodies of the vertebræ are very soft and are easily cut with the cartilage knife. The marrow spaces are increased in size and the bony trabeculæ greatly rarefied. The red marrow is entirely replaced by a grayish pyoid marrow having a distinct green color. After exposure to the air and drying, the grass-green color became more marked. On cutting into the vertebra direct connection can be seen in many places between the greenish tissue surrounding the vertebral bodies and the greenish marrow of the enlarged marrow spaces. The greenish tissue is firmly adherent to the surface of the vertebræ and cannot be stripped from it.

Careful and thorough examination of the head fails to reveal any evidences of periosteal thickening. There is no sign of the presence of orbital growths.

(The dorsal and lumbar portions of the spinal cord were removed.) Cord and meninges present no pathologic appearances. The bony wall of the canal is covered with a thin layer of greenish tissue.

The right tibia is split. Its fatty marrow is partly replaced by marrow redder than that found in either the sternum or vertebræ, but small points of pyoid, greenish-gray marrow are also present.

The section of the growths on the right and left clavicles shows that these are subcutaneous tumors having all the gross characteristics of lipomata.

Anatomic Diagnosis. The character and location of the greenish growths in connection with the changes in the red marrow form a sufficient basis for the diagnosis of chloroma.

OBSERVATIONS ON CHLOROMA SINCE 1893, BY DR. DOCK.

Since 1893 twenty-one cases of chloroma have been reported more or less fully. Two more were mentioned by Beneke and Drozda in discussions. Bramwell refers to probable cases known to him, as well as an interesting case described in his paper referred to in this article, in which some green lymph glands were found in the body of a patient who died of acute leukemia. Dr. Trevithick (personal communication) has heard of another case. No doubt some of the cases of symmetric tumor of the orbit, examples of which are frequently reported, are really chloromatous. I have heard indirectly of two unreported cases of chloroma observed in German clinics, in one of which there was leukemia. Many authors reporting cases of chloroma refer to the greenish color of the lesions in ordinary cases of leukemia. It is not necessary to discuss this

particularly, but I shall refer later to a most interesting case observed by Tuerk.

SEX, AGE, DURATION. In the present series of 22 cases there were 3 females, 19 males; or, in both series, 9 and 29, respectively.

The average age was 18.8 years, or three and one-half years older than in the former series. The average is raised by the occurrence of four cases in persons between thirty-eight and fifty-two years; 15 cases were less than twenty-five years old, 12 less than sixteen, 1 ten months.

The average duration was 5.5 months. In 10 it was four months or less, two each being stated as one and two months. In 1 case it was one year, another thirteen months, in a third one and a half years.

LOCATION OF THE CHLOROMATOUS GROWTHS. Regarding the seats of the peculiar green formations, the data in the later cases resemble in general those of the earlier series. Some part of the head was affected in all but two of the cases in which the examination was complete. In Bramwell's case and our own the skull was not examined. In Guembel's case the orbit, temples and periosteum of the base of the skull were not involved, but there were green masses in the dura of the brain. In Rosenblath's two cases the orbital tumors were not adherent to the periosteum, but seemed to proceed from the lids (in one also adherent to the optic nerve), and the cranial bones and periosteum were free from chloroma. In one of the cases the nasopharyngeal space contained green masses. In Sternberg's case the head showed no involvement. The most frequent seats in the head were the orbits (12 cases), usually involving the periosteum; the dura or sinuses (9 cases); temporal bone, especially in the auditory region (7 cases); the temporal fossa (8); less frequently the sphenoid (3); ethmoid (2); the choroid plexus (2); the nose, nasopharynx, maxillary antrum, pterygoid fossa, soft palate, gums, mastoid cells. The vertebræ were affected in 9 cases, usually in the periosteum of the bodies, sometimes in the dura, sometimes the periosteum of the processes, or the fat in the vertebral canal. The sternum was affected in 7 cases, in the periosteum either front or back, or eroding the bone (Rosenblath); sometimes the growth was continuous over the sternum, clavicles and ribs. The ribs were involved in 8 cases. The other bones were not so regularly examined, but green infiltrations or tumors were found in the periosteum of the sacrum, coccyx, iliac bones and the bones

of the extremities, in the diploe of the skull and in various flat and short bones. Chloroma was found in bone-marrow in 7 cases. The liver was the seat of green growths in 8 cases, the kidneys in 12, spleen 3, stomach once (Weinberger), intestines three times (twice in the appendix). The lungs, pleura, pericardium, endocardium and heart muscle (Dunlop) were rarely affected, also the serous and synovial membranes. The lymph glands were frequently involved, but in 1 case (Klein and Steinhaus) it is expressly stated that the lymph glands were without pathologic changes, the growths affecting the periosteum of the bones of the head and trunk, the kidneys, prostate, and bone-marrow of the femur. The cervical glands were most often involved (11 cases); less frequently the axillary, inguinal, submaxillary, mediastinal and bronchial glands, and those in the portal fissure of the liver, the lesser curvature of the stomach, around, above or behind the head of the pancreas, the prevertebral and mesenteric glands. Other locations were: the conjunctiva, tonsils, mucous membrane of the epiglottis, larynx, arytenoid cartilages, thyroid gland, thymus, bladder, prostate, urethra, ovaries, mammæ, pancreas, diaphragm, pelvic connective tissue and periosteum; the insertions of many muscles, as the temporals, intercostals, psoas and dorsal muscles; the brachial plexus, the adventitiæ of arteries and veins, or even all the coats of the vessels, the subcutaneuos tissue (Stevens) and the skin (Schmidt, Bramwell, Hitschmann).

The bone-marrow of the long bones was the seat of chloroma in 7 cases (Schmidt, Paviot and Gallois, Paviot and Fayolle, Rosenblath, Dunlop, Trevithick, Dock and Warthin), in several of which the flat and short bones were involved. In 6 other cases (Rosenblath II., Bramwell, Guembel, Weinberger, Sternberg, Tuerk) the fatty marrow was altered, either red or grayish-red. In some cases both kinds of change were present. In some cases the bones were not examined, in some others the examination was limited to a few bones, and inasmuch as the affection of the bone-marrow is not always symmetric we cannot be sure that in the cases with negative results there were no green foci at all in the marrow.

Of the associated changes it is not necessary to mention any except tuberculosis. This was found in the lymph glands in the cases of Schmidt, Rosenblath I., II., and Koerner. In the latter Lubarsch found tubercle bacilli in the faucial tonsil and several enlarged glands in the neck.

CLINICAL FEATURES. Most of the cases reported since 1893 show a general resemblance to the typical cases in the earlier series. Among 18 cases in which the clinical histories are given, early weakness was noted in 9, pallor or anemia in 11, exophthalmos in 11, swelling and eversion of the lids in another, deafness in 10, swelling of the temporal region in 9, swelling of the face in 3 more, enlarged lymph glands in 8, emaciation in 6, rapid pulse in 6. Pain was often a prominent symptom, and was most often felt in the head, eyes, teeth or ears, or in the hips or legs. Hemorrhages in the skin or mucous membranes were noted in 8 cases. Blindness occurred four times. The liver was enlarged in 3, the spleen in 7 cases. Albumose (Bence-Jones) was present in Weinberger's case. In both of Rosenblath's it was absent. In other cases there are no evidences for or against. It is noteworthy that in the 3 cases cited the bone-marrow was altered.

Some of the cases require more detailed reference.

In Lang's case, a man, aged fifty-two years, was seized with violent pain in the head and teeth three months before admission. At the same time a hard tumor appeared on the right cheek, with obstruction of the nares and pain in the right eye, with exophthalmos and blindness. The tumor became adherent to the skin, and ulcerated in the center. It projected into the palatine vault and the nose. It was removed by a resection of the maxillary bone, exposing a large cavity covered with green nodules, extending to the meninges. Owing to this the operation was not completed. The results were not known, as the patient disappeared.

In Bramwell's case the most remarkable feature was an eruption, beginning in the chest and spreading all over the body, consisting of flattened elevations from the size of a pinhead to that of a sixpence, often confluent. They were superficial, painless and for the most part of a slaty gray color, sometimes yellow in the centre. The gums were enormously swollen, firm, dark purple. The conjunctiva was infiltrated with a translucent, fleshy colored growth. The eruption on the skin in time became yellow, yellowish-green or distinctly green.

In Hitschmann's case there was also the combination of lesions in the mouth and skin. A man aged twenty-six years had a swelling of the cervical glands and enlarged spleen. The glands suppurated spontaneously, and showed no tendency to healing; the resulting ulcer had blue edges. The right tonsil was ulcerated. A bit

removed from the margin showed a lymphosarcomatous structure. In two months after the beginning of the observation the tonsils and the mucosa of the pharynx, nasopharynx, fauces and nares were greatly swollen. The blood then was normal. In two months more the skin became darker, of a pale-brown color, most intense over the cheeks and breast. A disseminated eruption appeared, with slightly elevated lesions, the size of lentils, of a grayish-green ("reseda") color, unchanged by pressure. The connective tissue of the eyelids became a pronounced grayish-green color; the scleræ also had a greenish tint. Other mucous membranes were pale red, transparent and finely nodular. Infiltrations formed in the soft palate, base of the tongue, and upper part of the larynx. The tonsils were replaced by nodular tumors. There were large, hard and almost immobile packets of lymphatic glands in the neck, axillæ and inguinal regions. The bones were tender. There was remittent fever. The blood then showed relatively many large lymphocytes, later considerable lymphemia, with anemia, poikilocytes, polychromatophilia and normoblasts. The patient died six months after admission. Grass-green new-growths were found in the tonsils, the mucosa of the gums, palate, nose, pharynx, larynx and bronchi, and in the cervical and mediastinal glands. The diagnosis of chloroma was made during life (1903), from the lesions in the skin.

In Schmidt's case there was a distinct green discoloration in the skin of the face and also on the body, but on the latter there were recent hemorrhages. There were also subcutaneous nodules.

The foregoing cases are interesting on account of the new features they add to the clinical picture of chloroma. It would increase too much the length of this paper to speak of the skin alterations in leukemia and allied conditions. Those especially interested will find a useful compilation in the monograph of Nékam,[1] while other interesting data are contained in the articles of G. Dieballa,[2] F. Pinkus,[3] and C. Audrey.[4]

In Guembel's case there was transverse myelitis, due to pressure of the chloromatous masses upon the cord, and in Rosenblath's

[1] Ueber die Leukaemischen Erkrankungen der Haut. Ergaenzungsheft, Monatshefte f. prakt. Dermatologie. Hamburg and Leipzig, 1899.

[2] Ueber einen mit Lymphocytose einhergehenden Fall von Sarkoma mult. Cutis, Wiener klin. Wochenschrift, 1897, p. 523.

[3] Ueber die Hautveraenderungen bei lymphatischer Leukämie und bei Pseudoleukämie Archiv f. Dermat. u. Syphilis, Bd. 1. pp. 37, 177; with extensive bibliography.

[4] Journal des maladies cutanées et syphilitiques, 1902.

first case there was degeneration of the right posterior column of the cord in the lumbar and dorsal regions from pressure.

Sciatica was a marked symptom in the cases of Rosenblath, Harris and Moore, and Klein and Steinhaus.

In Trevithick's case tumors were discovered in the breasts, in a girl aged thirteen years. The tumors became larger. "The left breast was composed of two very hard, globular tumors, each about the size of a hen's egg, freely movable over the deep parts, but adherent to the skin. The opposite breast was represented by three similar tumors." The mammary tumors "showed through the skin as being of a dark-blue color." The patient also presented the common features of pallor, proptosis, swellings in the temporal regions, subcutaneous hemorrhages, and nodules on the sternum and ribs. Postmortem: growths of bright-green color were found connected with various bones, in lymphatic glands, kidneys, liver, ovaries, pancreas, thyroid, dura mater and in the choroid plexus of the lateral ventricles.

Dunlop's case was the first one in which a diagnosis was made during life.

The patient, a boy aged five years, was fairly healthy up to a year before admission. For fully a year patches of ecchymosis were frequently noticed under the skin. In May, 1901, pallor was obvious, and for some months before that it was observed that any scratches on the body tended to suppurate. After a wetting and chill the boy became easily tired, called out in his sleep and snored. His appetite was poor and he grew steadily paler and more emaciated. In August his eyes became prominent, with dilated veins on the lids. In September he became deaf. On admission, September 30, 1901, he looked very ill, and was pale, with a waxy, yellow tint. There was a profuse petechial eruption everywhere except on the face, with two larger hemorrhages over the dura, spinal column, and the right knee, with a yellow discoloration, as of an old hemorrhage, on the right shin. Both eyeballs protruded, but the lids could be closed. There were a few enlarged glands under the jaw, on both sides, and in the posterior triangles of the neck and the groins. The heart dulness was enlarged; there were loud hemic bruits; pulse 110, irregular in time and force. The liver and spleen were not enlarged. The urine contained a small amount of albumin. The blood: hemoglobin, 32 per cent.; red blood corpuscles, 1,800,000; leukocytes, 24,500. Lymphocytes, large pre-

ponderating, 73 per cent.; polymorphonuclears, 17 per cent.; myelocytes, 5 per cent.; unclassified, resembling myelocytes, 5 per cent. A few nucleated reds.

The eyes became more prominent, the deafness worse. In the mouth a hard, purple swelling appeared on the hard palate, extending nearly the whole anteroposterior extent and from the teeth nearly to the median line, with discoloration to the median line. A smaller similar swelling appeared on the lower jaw on the right side, external to the teeth. In October a smooth, rounded swelling appeared in each temporal region, reaching behind to about half an inch in front of the pinna, and in front to the outer edge of the orbit, and apparently continuing into the orbit. On October 22d the diagnosis of chloroma was made. Photophobia came on. The upper eyelids became infiltrated, especially in their outer halves, with firm, smooth swellings which seemed to proceed from under the roof of the orbit in the region of the lacrymal gland and extend to the margin of the tarsal cartilage. In the left lower eyelid there was a tumor extending from canthus to canthus, appearing to come from under the lower margin of the orbit. The retinal veins were tortuous and moderately distended. In the right eye there was a minute extravasation of blood near the disk, and exudation into the disk and retina in both eyes. The leukocytes increased to 68,000 by November 2d. A pale, greenish-yellow tumor of jelly-like consistence made its appearance at the inner canthus of the right eye, and gradually advanced over the eyeball, covering its lower half. There was a smaller similar tumor in the left eye. Frontal pain became intense; the temperature rose to 101° F., the pulse to 140. The temporal tumors seemed to become smaller. Marked optic neuritis, with linear hemorrhages, developed in the right eye, still more marked optic neuritis in the left eye. By November 12th the tumors on the eyes covered both eyeballs. The corneæ were apparently destroyed. The temporal tumors were smaller. Leukocytes, 107,000; red blood corpuscles, 815,000; hemoglobin, 12 per cent. On November 15th the eyeballs were less prominent, leukocytes 123,000, waxy pallor of face and engorgement of veins striking, sordes on lips and teeth. After coffee-ground vomiting the boy died on November 16th.

The cases of chloroma with tumors of the orbit have close clinical relations with other orbital tumors and often result in sending the patient to an ophthalmologist. But the orbital tumors do not

suffice to make the diagnosis of chloroma. Besides leukemia without chloroma, lymphoma, lymphosarcoma and other formations often affect the orbits, causing exophthalmos in some cases. One of us (Dock) has had an opportunity of seeing a number of these cases clinically in the service of Prof. Fleming Carrow. The most interesting one is still under observation. Examination of an excised portion, by Dr. Warthin, shows a lymphomatous structure. Besides the orbital tumors there are growths in various parts of the body, including the roof of the mouth. The leukocytes number 10,000, 40 per cent. being lymphocytes, 7 per cent. eosinophiles, but without the finer details of lymphatic leukemia. Risel has given a useful *résumé* of the literature of this part of the subject.

The cases without swellings in the orbit and temporal region are of special interest in connection with the one now reported. In Weinberger's case, a boy, aged fifteen years, had rigidity of the skin and weakness of the lower extremities, following scarlet fever. The cervical and inguinal lymph glands became enlarged; there were hemorrhages from the nose and gums and in the skin, hemorrhage from the right ear, deafness, splenic tumor, dilatation of the heart, and fever. The urine contained Bence-Jones albumose. The growths involved the lymphatic tissue almost universally, the dura and serous membranes, the liver and kidneys, and the periosteum of the vertebræ. The tumors penetrated the vertebral canal and compressed the cord.

In Sternberg's case, too, the skull was not involved, but all the superficial and deep lymphatics, especially those of the floor of the mouth, were affected. The patient died of intercurrent disease (putrid bronchitis as the result of the perforation of a softened anthracotic bronchial gland into the esophagus and bronchus), so that the case really presents an early stage of the disease and seems to bear out the author's belief of a primary focus in the soft palate and pharynx.

A marked tendency to deafness and other ear symptoms was shown by the later cases, as it was in the earlier ones. One of the most striking examples was shown by the patient of Koerner. A boy, aged six years, became deaf. He also had headache and double exophthalmos. Both abducent nerves were paralyzed, the cutaneous veins of the forehead distended; both temporal regions were swollen. There was choked disk. The tympanic membranes bulged; they were pale grayish-yellow. The left mastoid was tender,

but not swollen. Considerable pus was evacuated from both tympanic cavities. The diagnosis was phlebitis and thrombosis of both cavernous sinuses. After a fresh puncture of the left tympanic membrane, with elevation of the temperature, a mastoid operation was performed. The patient collapsed, but revived, and the operation was finished without exposing the lateral sinus. Death occurred five weeks later, without rise of temperature, but with frequent pulse (144) and respiration (66), and with rigidity of the neck. Postmortem, no phlebitis was found, but instead a marked chloromatous growth involving the sinuses, the base of the skull, and other parts. Koerner analyzed the ear conditions in all the (20) cases of chloroma available, with great thoroughness, and found ear symptoms in 10.

The literature of the ear complications in leukemia has grown considerably since I referred to it in my former paper. For recent cases see Kast,[1] Kuemmel,[2] Schwabach.[3]

Out of the protean symptoms of chloroma cases we can separate three sets of conditions: the mechanical results of the green growths, causing many symptoms both objective and subjective (exophthalmos, visible tumors, pain, deafness, etc.); the toxic symptoms, as weakness, fever, emaciation; and the blood symptoms, such as pallor, hemorrhages, and alterations of the blood itself.

The latter requires more particular consideration, and more especially so because of the effort I made in my previous article to show a relation between chloroma and leukemia. I need only allude to the resemblance of many of the symptoms of chloroma to those of leukemia, especially of acute leukemia. The condition of the blood, however, is the criterion of the leukemic change, and its condition in chloroma cases requires more detailed examination.

THE CONDITION OF THE BLOOD. Ever since Recklinghausen assigned chloroma to the leukemic group of diseases the blood has been the most important single clinical feature, but owing to the imperfect application of blood examinations in general, and failure to appreciate the nature of cases during life, the blood has not yet received as much attention in chloroma as it deserves. In 5 of the present series of cases the blood was not examined (Lang, Koerner,

[1] Deutsche med. Wochenschrift, 1894, Beilage 27, p. 187.

[2] Ear Disease in Leukemia, German Otological Society, 1896; Archives of Otology, vol. xxvi. p. 115.

[3] Ueber Erkrankung des Gehoerorg. bei Leukämie, Zeitschrift f. Ohrenheilkunde, Bd. xxxi. p. 103.

Paviot and Gallois,[1] Harris and Moore, Hichens). In 2 it was not fully examined, or, at all events, not fully reported. In 1 of these —Schmidt—it is said the blood showed simple anemia; in the other (Paviot and Fayolle) there was said to have been leukocythemia of 1 to 3 or 4. This latter statement is not so definite as that of Ayres, who described leukocytosis in his case without increase of "small lymphocytes and those white cells characteristic of splenic and myelogenic leukemia." More prolonged examinations might have modified the descriptions in both cases. In Tuerk's case there was leukopenia with severe anemia. In the other 13 cases the conditions were more characteristic of leukemia, though in 1 the leukocytes were not increased. This was the case of Bramwell, in which there were 8000 leukocytes per c.mm., with 95 per cent. of lymphocytes, "chiefly large lymphocytes, with large nuclei and clear, non-granular protoplasm. During the month the patient remained in the hospital the blood condition remained practically the same." As Bramwell remarks, "the mere fact that the leukocytes were not increased did not exclude leukemia." In 10 cases, according to the reporters, the blood resembled that of acute leukemia or acute lymphocythemia. Examining these cases in detail we find in Rosenblath's first case: red blood corpuscles, 1,000,000; leukocytes, 300,000. "The small mononuclear lymphocytes appear in small numbers, and the polymorphonuclear neutrophiles are scanty in proportion to mononuclear forms of various sizes, the smallest of which only slightly exceed the red corpuscles, the largest reach a considerable size. The protoplasm is usually reduced to a narrow ring, the outer layer of which often stains deeply with methylene blue. Only in the large forms has the protoplasm a greater extent. The nucleus stains rather faintly, shows usually a granular or filamentous network, is round or oval, usually simple, but sometimes double. There is moderate poikilocytosis, only an occasional nucleated red corpuscle." In Rosenblath's second case the red corpuscles varied from 3,700,000 to 2,300,000; the leukocytes, 40,000 to 58,000; later to 37,000. There was distinct poikilocytosis, a nucleated red cell, usually a normoblast, in almost every preparation. The leukocytes resembled those in the first case. The polymorphonuclear neutrophiles were considerable at first, but

[1] Paviot and Gallois are, of course, in error when they intimate that the blood had not been examined in any of the cases before their own.

later were reduced to one-quarter or one-fifth of all leukocytes. Small lymphocytes were scanty, eosinophiles very rare. Sutherland's case (observed in 1893) had 2,200,000 red corpuscles. The leukocytes a few hours before death were "180 to a field. There was a great increase of lymphocytes, varying in size." In Stevens' case the blood count was: red corpuscles, 766,000; leukocytes, 491,600; hemoglobin, 15 per cent.; small lymphocytes, 94.6; large lymphocytes, 1.4; polynuclears, 2.7; eosinophiles, 1.3. In Guembel's case the condition of the blood during life is not reported. Postmortem, the red and white corpuscles after sedimentation were about equal. "The great majority of the leukocytes belong to the group of large lymphocytes (Ehrlich); the rest are small lymphocytes. There are two kinds of the former. In one, two or three times as large as a red corpuscle, there is a large nucleus and, as a rule, little non-granular protoplasm. The nucleus is usually vesicular, only the nuclear membrane and chromatin network stain intensely, but some forms occur in which the whole nucleus takes blue intensely. The nucleus is usually oval and excentric, but not rarely is indented, so that it has a saddle-bag form. Less frequent are cells of the same size, but with a pale, indistinctly outlined nucleus, usually resembling a shadow, and often not possible to recognize. This is the form represented by Dock as A, Fig. B. Polymorphonuclear cells are rare, also eosinophiles, and these have nuclei like those of the lymphocytes described." Normoblasts, megaloblasts and Charcot's crystals were not found in the blood. I have not been able to find the full report of the blood in Sternberg's case, which was to have been published in detail by Obermayer. In another place[1] Sternberg mentions it as giving the picture of acute (large celled) lymphatic leukemia. In Weinberger's case the red corpuscles ranged from 4,500,000 to 3,200,000; leukocytes, 13,000 to 72,000. In the beginning there were 86 per cent. of large lymphocytes, few polynuclears and eosinophiles, no mast-cells. With 72,000 leukocytes the large lymphocytes were still in the majority. "The blood was in all respects like that of acute leukemia." In Trevithick's case there was extreme anemia, but no count was made. "The blood was first examined three weeks before death. There was then great increase of white cells. . . . On comparing the films made at that time with those

[1] Verhandlungen des Deutschen Patholog. Gesellschaft, 6 Tagung, 1903, pp. 30-33.

prepared shortly before death it was evident that the number of white cells in the blood increased very rapidly. The change, in fact, resolved itself into an enormously great and rapid increase of mononuclear cells. Among this crowd of mononuclear cells, which in the later stages became approximately equal in number to that of the hemocytes, there appeared a considerable number of bodies which, after careful examination, I believed to be degenerating nuclei derived presumably from defunct cells. These bodies varied in size and shape, but in some cases their dimensions were surprisingly large, and I saw several that possessed a diameter equal to six times that of the neighboring red blood corpuscles." These bodies resembled some in a preparation from a case of acute leukemia. "Some of the intact mononuclear cells found in the blood attain exceedingly large dimensions. Great variation in size is noticeable, and they seem to be distributed in groups." The illustration given in Trevithick's article shows many cells such as occur in our present case of chloroma as well as in many cases of acute lymphocythemia, while the degenerated cells so clearly described by the author are such as occur in leukemias of various kinds, and were particularly marked in a case of chronic small-celled leukemia reported by Dock.[1] In Hitschmann's case the blood, late in the disease, contained "relatively many large lymphocytes, later considerable lymphemia, with anemia, poikilocytosis, polychromatophilia, and normoblasts." In our own case, while the blood shows some differences as compared with many cases of acute leukemia hitherto reported, it has probably many counterparts in the latter disease. In its eosinophile cells and myelocytes it differs from Dock's (1893) case and forms a transition from many of the other cases to those of Dunlop and Klein and Steinhaus. In Dunlop's case the blood at first showed: hemoglobin, 32 per cent.; red blood corpuscles, 1,800,000; leukocytes, 24,500. The differential count was: lymphocytes, large predominating, 73 per cent.; polymorphonuclear, 17 per cent.; myelocytes, 5 per cent.; unclassified and transitional forms resembling myelocytes, 5 per cent.; a few nucleated red cells. The red cells fell in six weeks to 815,000; hemoglobin, 12 per cent.; the leukocytes rose in the same time to 123,000. Dr. J. S. Fowler has described the blood in this case,[2] and

[1] Moscow International Medical Congress, University Medical Magazine, March, 1898.
[2] International Clinics, 1903, series 13, vol. iii. p. 225.

has given a somewhat different count. For example: October 5th, leukocytes, 25,000; small lymphocytes, 15; large, 48.5; polynuclear, 31.5; eosinophiles, few; myelocytes, 5. November 11th, leukocytes, 64,000 (Dunlop gives the number November 12th as 107,000); small lymphocytes, 15.5; large lymphocytes, 53.5; polynuclear, 16; myelocytes, 15; no eosinophiles in the last two counts two weeks apart. Divergences in leukocyte counts by different observers are, of course, very common, depending partly on staining technic, partly on different conceptions of certain cells, but the discrepancy in the polynuclear counts in this case is hard to understand. Nevertheless, we can accept the reports as showing a still more distinct transition toward myelocythemia than was present in our own case. A still greater departure from the lymphocythemic type was present in the case of Klein and Steinhaus. Here the leukocytes rose from 20,000 to 41,000. Lymphocytes varied from 40 per cent. small, 10 per cent. large, to 19 per cent. small, 47 per cent. large. Myelocytes varied between 16 and 32 per cent. The report does not describe the rest of the cells, but it is obvious that the case was not an ordinary one of mixed-celled leukemia, as the authors seem to intimate. A more distinct example of the latter occurred in a case of Tuerk's,[1] which I have excluded from the list of chloroma cases for the same reasons that made me exclude some other probable cases reported under the title of leukemia. In this case, a man, aged thirty-eight years, had hemorrhages from the gums, weakness, anemia, ecchymosis in the retina, enlarged spleen and pain in the sternum. The blood examination showed: red corpuscles, 1,060,000; leukocytes, 42,000; hemoglobin, 19. Differential count: 14.75 lymphocytes, 32 polynuclears, 47 myelocytes, a few eosinophile myelocytes, no mast-cells. In seven days the blood fell to: red corpuscles, 500,000; leukocytes, 58,000; hemoglobin + 10; lymphocytes, 18; polynuclears, 37; myelocytes, 37; 1 normoblast. Postmortem there was diffuse grass-green infiltration in the bone-marrow of the vertebræ, ribs, sternum and proximal ends of both femurs. The upper part of one humerus had reddish-gray marrow, the other long bones fatty marrow. The retroperitoneal glands were green. Here we miss the full picture of mixed-celled leukemia, especially eosinophile and mast-cells, normoblasts and megaloblasts. But the case has an important bearing on the ques-

[1] Wiener klin. Wochenschrift, 1903, p. 333.

tion of the nature of chloroma that must be considered in another connection, and illustrates the diversity of blood pictures in leukemia, which is suggested in the relatively small number of cases of chloroma. Investigations by many observers are putting it beyond question that besides the two main groups of leukemia there are many varieties, as I have held for many years. The exhaustive and authoritative article of Dr. A. O. J. Kelly, presented to this Association a year ago, makes unnecessary a repetition of the evidences now at hand.

While it is obvious that in many cases of chloroma the blood resembles that of acute leukemia, and while the symptoms are often acute, we need more exact observations. The blood examinations, as a rule, were not made early enough to determine this fact—a difficulty that occurs sometimes in non-chloromatous "acute" leukemia. There are a few interesting observations already available in chloroma. In Rosenblath's first case there were 300,000 leukocytes at the first examination, three and one-half months after the beginning of symptoms. In the second case of the same author the blood was first examined eleven days after the first symptoms, and contained 40,000 leukocytes per c.mm., increasing in eight days to 58,000, but in two months the number was lower—37,000. The patient died ten days later. In Weinberger's case the leukocytes rose from 20,000 to 72,000 in two days. In Dunlop's case they increased from 24,500 to 123,000 in six weeks. In this case petechiæ occurred early, suggesting an alteration of the blood. In our own case the symptoms indicate an anemia very early. It is impossible to tell what changes the blood passes through, but the extreme oligemia suggests grave failure of the red blood-forming organs, which might have been due to the overgrowth of the normal tissue by the morbid process, which sooner or later produced the excess of leukocytes in the peripheral blood. There was no distinct change in the number of leukocytes under observation, and it is, of course, as possible that leukocytes were more numerous at some previous period as that they rose just before the end.

From the data now available the relationship of chloroma to leukemia seems settled. That the full picture of leukemia does not always develop in all cases is to be expected. That qualitative changes will occur in the blood, and that quantitative changes will appear in regard to certain common cell forms, there can be little doubt. But assigning chloroma to leukemia of course leaves un-

settled many problems. One of the first questions that arises in this connection is with reference to lymphocytosis in so-called lymphosarcoma and other diseases not yet positively identified with leukemia, but with many indications of relationship. This, as well as some other questions, can only be determined by the discovery of the etiologic factors, though careful clinical observation and study of the blood may materially further the subject before that consummation has been reached.

Two other questions raised by chloroma require some attention: the nature of the color and the histologic position of the new-growth.

THE COLOR OF CHLOROMA. The later cases of chloroma have not advanced our knowledge of the nature and cause of the green color. No extensive examination seems to have been made, probably because the most obvious explanations had been tried and found wanting in the earlier cases, where the ordinary chemical and physical methods were applied for the detection of possible color principles. There is apparently a difference in behavior of the color under comparatively simple conditions. Most observers state that the color fades quickly on exposure to the air (or light), as during the autopsy; but Dr. Warthin noticed an increase in the depth of the color in our last case, possibly from drying. Almost all say the color fades in various preserving solutions, and does not go into solution in the fluids. Risel, for example, found that the color was not preserved in Kaiserling's method, in which the greenish color of tuberculous foci in the same specimens retained their peculiar tint. Alt found that the tissues retained their dark grass-green color in formol solution, and the fluid itself was of a dirty-green color and looked fatty. Allowing the fluid to evaporate, large droplets of dark-green, oily substance remained, with many octahedric crystals, like calcium oxalate. The account suggests bile coloring matter, but no mention of jaundice is made.

That the color is not a postmortem phenomenon appears from some observations during life in the older series, as well as those of Lang, Bramwell and Hitschmann in the present one. On the other hand, an origin from broken-down blood pigment is suggested by certain observations. Risel found hemosiderin granules in the tumors, and referred these to breaking down of red blood corpuscles, but he ascribed the green color not to these granules, but to some other substance of hematogenous origin. He compared the process to the "green granular pigment" found in the dog's placenta.

explained by Lieberkühn and Strahl as originating in extravasated blood. Lubarsch found the color a deeper green along the sinuses in his case—"in fact, a diffuse green coloration of the sinus walls was observed in the vicinity of the chloromatous tissue." Of course, this does not prove that the blood made the green color, any more than that a pigment of some other origin was deposited in those parts. Guembel[1] quotes some experiments of H. Ruecker on blood pigments, to which he might have added some other suggestive experiments, cited in the same thesis, showing the possibility of deriving green coloring from blood. This, of course, follows from the changes in subcutaneous hemorrhages, and the observations on such processes by Langhans and others.

Risel, Lubarsch and Weinberger made it practically certain the color is not of bacterial origin, while Lubarsch was unable to find pigment granules in either sections or fresh preparations. Sternberg's results with Sudan III., showing fat droplets in the lymphocytes, does not prove that the color is due to an ordinary fat.

Paviot and Gallois made some tests of chloroma tissue with guaiac, which led them to the conclusion that chloroma contains an oxidizing diastase. They also found, however, that a similar reaction occurred with other tissues of rapid growth, confirming the conclusion of Klein that the reaction depends on relative youth of the cells.

The suggestion of Schmidt that the color is due to the shape of the cells has not found any confirmation.

Bramwell raised the question whether the color is due to the same causes in all cases of chloroma. He considered it possible that it might be due to different causes in different cases, and that it might even be due to different pathologic conditions. He also thought there might be cases of chloroma without green tumors and no green lesions; "that the green discolorations, though they had hitherto been considered to be essential and characteristic features of the disease might in some undoubted cases of chloroma be absent." These suggestions are not as paradoxic as they seem. They show the danger of making such a feature as color the basis of classification, especially when pertinent cases are few and the color itself is so elusive and so difficult to analyze as in chloroma. It is true that in order to deserve the term chloroma there should

[1] Zur Kenntnis des Haematoporphyrin und seiner Derivate, Inaug. Dissert., Strassburg, 1901.

be a green color, but if the green color is associated with a definite structure it might be possible to make the diagnosis even if the color were absent, either naturally or as the result of preserving methods. To take a clinical example, not every chlorotic has a greenish tint, as Virchow pointed out long ago. In a number of recent cases there were new-growths of ordinary color besides the green ones, as there were in some of the old ones (*e. g.*, Dock, 1893). In Schmidt's case some lymph glands showing the structure of malignant lymphoma were removed eight months before death, and showed no trace of green color.

In Koerner's case some of the tumors were not green, though they had the same structure as the green ones. This was also true in Weinberger's case, and in a case of acute leukemia Bramwell found a few green lymph glands. It is therefore certain that the green color is not present in all the lesions in chloroma, and possibly that it is not present in the beginning. That the color occurs in other processes appears from the cases of Klein and Steinhaus and Tuerk, the earlier cases of leukemia with green lesions being left out of consideration because of a certain imperfection in the blood examinations. But the various observations of pure lymphocythemic chloroma and the two cases just mentioned make it certain that whatever the green color is due to it is not confined to any one particular histologic structure.

It is interesting to note that in Trevithick's case the heart clot was green, but less so than the new-growths. In Guembel's case the sedimented leukocytes were green, and there were greenish clots in the heart, but in many other cases, including Rosenblath's with 300,000 leukocytes, green clots are not mentioned.

VIEWS OF AUTHORS ON THE CLASSIFICATION OF CHLOROMA.

Most authors agree upon the main histologic details of chloroma. There are certain differences regarding the size of the cells that make up the growths, some describing them as small, others large, others even as very large, but this difference is probably chiefly a matter of standards. On the other hand the interpretation of the structure is not always the same. It will be interesting to pass some of the explanations in review.

Lang made a variation when he described the growth in his case as a myxosarcoma or chloromyxosarcoma. I see no reason, how-

ever, from excluding it from the statistics of chloroma, as I did in the case of Bock in the earlier series.

Schmidt thought the process, like that in leukemia and pseudoleukemia, primarily affected the lymphatic apparatus and the closely related bone-marrow. He thought the disease was without metastases.

Lubarsch thought the tumors so much like lymphoma and lymphosarcoma, histologically, that but for their green color the possibility of anything but lymphoma would never have been entertained. But he would separate chloroma, as well as lymphosarcoma and tumors of that kind, which seem to have a toxic or infectious origin, from sarcoma and other autogenous tumors. "The former are merely a manifestation of a general diseased condition of the organism. Though they may develop in large numbers in the body, each tumor must be looked upon as a primary condition and not as a metastatic formation depending on the dissemination of some primary autogenous growth; while they usually have a predilection for lymphoid tissue, they have been found in other parts of the body." Lubarsch, like most recent authors, agrees that Dock was right in emphasizing the differences between ordinary periosteal sarcoma and chloroma.

Paltauf,[1] who discussed the subject in 1897, placed chloroma, with leukemia, pseudoleukemia and myeloma, among the lymphomata or lymphosarcomata in the sense of Kundrat, and more definitely under lymphosarcoma as an appendix, and he suggested that it should not be spoken of as a sarcoma. Since the view of Kundrat has strongly influenced many in their views, and yet has not been universally accepted, it may be well to explain that author's conception of lymphosarcoma.[2] According to Kundrat, lymphosarcoma arises from lymph glands or from the follicles of a mucous membrane, always from a group of follicles; and though it may long remain localized there, it in time passes into other lymph glands or follicles, breaking through the capsule and infiltrating the surrounding tissue. The infiltration proceeds more or less rapidly according to the tissue affected, most rapidly in loose tissue, under the surface, on and in mucous membranes and serous membranes, so that in hollow organs large areas are involved, but usually not lead-

[1] Ergebnisse der allg. Path. und path. Anat., III. Jahrg., 1896.
[2] Ueber Lymphosarkomatosis, Wiener klin. Wochenschrift, 1893, No. 13.

ing to stricture, rather to dilatation. Distant locations are involved, somewhat resembling metastasis in other tumors, but never causing nodules, rather infiltrations. One reason why Kundrat rejected the idea of metastasis is that the usual seats of metastatic cancers and sarcomata are not affected—that is, the internal organs —but rather the intestinal canal. Metastases by way of the blood circulation rarely occur, also ruptures into bloodvessels; the latter are more likely to be compressed and obstructed. However, secondary thrombi occur. Unlike leukemia and pseudoleukemia, lymphosarcoma does not have diffuse infiltrations of the liver and spleen. These organs are more likely to be small, in consequence of marasmus. The bone-marrow is also not affected.

This conception of Kundrat seems difficult or even impossible to accept literally, on account of the numerous connecting links between it and the very diseases that Kundrat separated from it, and also because of the older and equally unsatisfactory use of the term lymphosarcoma.

Rosenblath emphasized the difficulty of classifying chloroma among lymphomata on account of the tendency of the latter to remain within the capsule of the gland and not form metastasis. "In chloroma even the tumors of the orbit, which seem at first glance to act like lymphomata, are quite different. They have no capsule, and grow through fat, nerves and muscles. The majority of the other larger tumors are closely united with the periosteum and grow diffusely." Clinically and microscopically he thought chloroma grows very differently from leukemic and pseudoleukemic lymphomata, but he recognized the intimate relationship between chloroma and leukemia, and admitted that the histologic structure differed from that of sarcoma.

Risel, who made the anatomic examination in one of Rosenblath's cases, agrees in general with the points I made in my first report against the sarcomatous nature of the process, and emphasizes the clinical and anatomic reasons for assigning it to the group of leukemia and pseudoleukemia, and with the histologic structure of lymphosarcoma or lymphoma. But he prefers the term chloroma as less likely to involve error. According to him one could suppose the disease began in the prevertebral lymph glands, or perhaps in the lymphatic tissue of the bone-marrow. He also admitted the possibility, in his own case, of an origin in old, caseated, retroperitoneal glands. He thought the blood condition was not sufficiently

known to place the disease in a definite group of leukemic processes.

Dunlop, too, thinks that lymphosarcoma is perhaps the best term to apply to "the growths found in chloroma resembling on the one hand lymphomata in their structures, and sarcomata in the fact that they arise from the periosteum and that they spread by metastasis." This is of course somewhat different from the conception of lymphosarcoma held by some of the authors previously quoted, and not altogether in line with recent views on the pathology of sarcoma.

Guembel described the tumors in his cases as lymphomatous, having many resemblances to bone-marrow. The cells were mononuclear large lymphocytes, like those in the blood and bone-marrow, lying in a scanty connective tissue, evidently that of the original tissue. The tumor was not circumscribed in any part, but spread out irregularly, accordingly to the denseness of adjacent tissue. The tumors were poorly vascularized, without evidences of new-formed vessels. Admitting the resemblance of the tumor to sarcoma, he points out that chloroma is essentially limited by mechanical conditions as regards its spread, unlike the unlimited growth of sarcoma. Another point is the impossibility of finding a primary growth. Other points of difference are: The absence of giant cells, of bone formation, of characteristic circumscribed metastases in internal organs. The cells of the tumor he too thinks are the same kind as the majority of those in the blood, the bone-marrow and the splenic pulp. "All the lymphoid tissue in the body was increased. In the bone-marrow the normal elements were lessened or absent, but the large lymphocytes much increased." This led him to place the primary seat in the bone-marrow. Moreover, the tumors, clinically first demonstrable and anatomically apparently the oldest, are with rare exceptions near the skeletal system—*i. e.*, in tissue nearly related to bone-marrow. He considered the tumors as secondary formations, beginning probably in lymphadenoid tissue and growing out from there. "Inasmuch as chloroma remains separated from the lymph glands by their capsules, it is evident that the change in the glands is the expression of the general disease, that the tumor does not originate in them. The term lymphosarcoma is therefore not applicable." He notes the close resemblance that chloroma cases have to acute leukemia in their respective terminal stages.

Trevithick rejected the idea of sarcoma on account of the symmetry of the lesions, the relative position of the organs invaded, the irregularly disorderly disposition of the individual invading cells, and the marked absence of vascularization. He described the cells in the various tissues and found them identical. The bodies are irregularly polygonal, the nuclei large. In the lymphatic glands he found many vascular, presumably lymphatic, spaces, wherein the endothelium is evidently undergoing immense hyperplasia. These he thought had an important part in the morbid condition.

Hichens, on the other hand, who has a somewhat imperfect idea of my own reasons for objecting to the term sarcoma, thinks that the erosion of bone which occurs in some cases is suggestive of sarcoma—which, of course, might be said quite as truly of aneurysm of the aorta—and suggests that lymphatic leukemia is a fluid sarcoma of the hematopoietic system and that chloroma is only another manifestation of the same disease characterized by solid deposits.

Sternberg considered the process a lymphosarcomatosis in the sense of Kundrat and Paltauf. His patient probably died early in the disease, before the process had spread beyond the lymph glands. He thinks there are certain relations between pseudoleukemia, leukemia, and lymphosarcoma, though the anatomic separation is possible. To him the difference depends on the presence or absence of heterotopy. The growths in the dura and periosteum he considered evidence of lymphosarcoma rather than lymphoma.

Klein and Steinhaus were the first to report a marked departure in the histology of chloroma. In films spread from the spleen, bone-marrow and the green tumors they found that most of the cells instead of being lymphocytes were neutrophile cells, mostly myelocytes. The rest were lymphocytes, or in the bone-marrow, these with eosinophiles and red corpuscles. Sections showed the same kinds of cells. Accordingly, these authors would remove chloroma from the lymphosarcoma group and place it among the leukemias. The green color they would give a subordinate place among the characteristics of chloroma, and would lay most stress upon the localization, the great aggressiveness, the tendency to infiltration and the rapid course.

Weinberger says that in his case the anatomic diagnosis of Weichselbaum was lymphatic leukemia, leukemic lymphoma, chloroma. He thought it differed from lymphosarcoma of Kundrat in that the

lymphoid nodes, notwithstanding their extent, remain in the place of primary growth, and do not infiltrate the adjacent tissue. It resembles lymphatic leukemia in the nodular foci in the mucous membranes, the serosa, peritoneum, liver, spleen and bone-marrow, and in the blood picture.

Tuerk objects to the separation of leukemia, and especially lymphatic leukemia and lymphosarcoma, and insists on the occurrence of transition stages from one to the other. According to him, chloroma is a local lymphosarcoma, a malignant lymphoid hyperplasia, with or without lymphemia. He alludes to the intramuscular infiltration as an evidence of the malignant character of the disease. The differences in blood pictures can be explained by the affection of the bone-marrow.

While there are some contradictions and differences of opinion regarding the growths among those who have examined cases of chloroma, I think it can be said that histologically most of them have a structure that can best be compared with that of the leukemic lymphomata. That certain variations occur, however, seems beyond question, and I believe that Dr. Warthin's examinations in this case reveal some important demonstrations of this fact.

MICROSCOPIC EXAMINATION BY DR. WARTHIN.

Preparation. In the preparation of the material for microscopic examination alcohol, formalin, mercuric chloride, Zenker's, Müller's and Flemming's were used as fixing and hardening agents. Some of the material was also examined in the fresh state. A portion was fixed and embedded in formol-agar. The greater part was embedded in paraffin. Celloidin embedding was used for a few tissues and for the material fixed in Flemming's. A great variety of staining methods was employed: hematoxylin and eosin, Van Gieson's, carbolthionin, Wright's, Romanowsky's, Jenner's, kresyl-echt-violet, polychrome methylene blue, triacid, Weigert's fibrin, Weigert's yellow elastic, Mallory's reticulum, etc. Sudan III. was used for fresh material and for sections cut in formol-agar. Potassium ferrocyanide and HCl were used for the iron test. Ebner's fluid was used for decalcifying the vertebræ.

Prevertebral Green Tissue. Sections cut at right angles to the surface of the prevertebral green tissue show that the upper portion consists of adipose tissue and the lower portion of the dense connective tissue of the prevertebral fascia and periosteum, both being densely infiltrated with cells that in general correspond to the cells found in the blood as described above. The infiltration of the denser connective tissue is arranged in rows or cords of cells extending in the

lymph spaces and bloodvessels between and parallel to the dense fibers of the reticulum. In the adipose tissue the infiltration is more irregular and the cords of cells proceed in all directions between the fat cells. In many places the latter are atrophic or have entirely disappeared, their place being taken by masses of new cells. In the denser parts of the periosteum the cells are often arranged in rows of single file, and are elongated, often spindle-shaped. In the looser fat tissue and in the lymphatics and bloodvessels the cells are usually round or oval. The majority of the nuclei are somewhat larger than a red blood cell, stain moderately deeply, or are pale and have a distinct, finely filamentous network of chromatin. In general the nuclei are round or elongated according to the situation in which they are found, but they are also frequently indented, saddle-bag shaped, bilobed or divided completely into two. In the cells having two nuclei the latter are often somewhat smaller than the nucleus of the mononuclear forms, stain a little more deeply and have coarser chromatin threads. The appearances sometimes suggest a recent mitotic division.

The majority of the cells of the infiltration possess a small rim of protoplasm varying in thickness, and usually more prominent at one side of the cell. Other cells have a more abundant protoplasm, but many show no protoplasmic rim at all. On the whole the proportion of cells showing a distinct protoplasmic body is greater in the infiltration than in the blood. The most striking feature of the infiltration is the fact that the majority of cells having a well-marked protoplasmic rim contain *eosinophile granules*. These granules for the greater part are in all respects apparently identical with the granules of ordinary eosinophile cells; they are of the same size, possess the same staining reactions and in unstained fresh sections appear as greenish-yellow, refractive granules. In some cells the eosinophile granules are fewer, smaller and paler. A small proportion of cells have a neutrophile granulation and a smaller number still have a distinct basophile granulation. Apparent transition forms between these are sometimes found. In those cells possessing no granulation the protoplasmic rim is either colorless or at times stains faintly with the nuclear stain, at other times with eosin. Apparent transition forms are seen between the cells without granulation and those with numerous eosinophile granules. In the majority of fields the number of the mononuclear eosinophiles is so great that a red tint is given to the section. In some fields every cell may show eosinophile granulation; few fields exist without some eosinophile cells, while in the great majority of fields the proportion of eosinophile cells by actual count runs from 50 to 75 per cent.; while from the numerous transition forms found everywhere there can be no doubt that the eosinophile cells are derived from the large "lymphocytes" of the infiltration, it is impossible to distinguish those eosinophile cells having an abundant protoplasm from the eosinophile myelocyte. Few polymorphonuclear eosinophiles are found in the infiltration. In the denser portions of the periosteum the number of eosinophiles is not so great as in the looser connective tissue and adipose tissue. Many of the spindle-shaped cells in the former,

however, show eosinophile granules. On the whole, the eosinophile cells show no especial grouping with reference to the bloodvessels.

Mast-cells are few or entirely absent. Few polymorphonuclear leukocytes are seen, and are easily distinguished by their more deeply staining nuclei. Some of these are also eosinophilous. Typical small lymphocytes are also rare. No giant cells or phagocytes found. Few mitoses seen (this may be accounted for by the long time elapsing between death and autopsy), although numerous appearances suggest clumped mitoses. The transition forms of indentation, constriction and complete division of the nucleus suggest amitotic division. Mitoses were twice seen in cells with eosinophile granulation.

Evidences of degeneration of individual cells are present in the form of pyknosis and karyorrhexis, but definite areas or centers of degeneration are not seen. A few cells containing small vacuoles were found.

No pigment granules are present in any of the cells of the infiltration. The iron test was negative in so far as these cells were concerned. The treatment with osmic acid was also negative. The staining of fresh sections with Sudan III. showed fat droplets in the cells of the reticulum, but not in those of the infiltration. In some areas a very slight diffuse orange was imparted to the cell protoplasm. In the fresh sections the eosinophile granules were seen distinctly as refractive, shining granules having a distinct greenish-yellow color. No other evidence as to the source of the green color of the tissue could be obtained.

There are no positive evidences of the formation of new bloodvessels in the infiltrated tissues. On the other hand these appear poorly vascularized, the bloodvessels being apparently those of the original tissue and more or less filled with cells of the same type as those of the infiltration. Very few red cells are seen in the vessels. Under the high power red blood cells may be seen in small numbers scattered throughout the reticular spaces in company with the new cells. It is difficult to decide whether these represent small hemorrhages or whether the red cells lie in bloodvessels which are more or less obturated by the new cells. Evidences of red-cell destruction are present in some places, the red cells lying in association with the new cells showing fragmentation, or are represented by granules of iron-containing pigment. As mentioned above, no red cells or blood pigment of any kind occur within the cells of the infiltration. The reticulum of the infiltration is chiefly or wholly that of the original tissues, but there is undoubtedly some increase of reticulum both in the periosteum and denser fascia as well as in the adipose tissue. There is also some thickening of the walls of the medium- and larger-sized bloodvessels, and an endothelial proliferation of the smaller. As a rule, the walls of the large vessels show but little or no infiltration by the new cells.

The infiltration behaves in all respects as a *tumor infiltration*. The original tissues are either crowded apart, compressed or have become atrophic. Such changes are seen particularly in the case of nerve trunks and ganglia. The

spinal nerves and ganglia show especially the results of such infiltration and compression. In the case of ganglia that are completely surrounded by the infiltration the ganglion cells are atrophic and present various appearances of degeneration. The nerve trunks show an infiltration along the bloodvessels and lymphatics.

The general picture presented microscopically by sections of the prevertebral green tissue is that of a *tumor infiltration in which the cells are of the type of large lymphocytes or myelocytes, the majority showing eosinophile granulation.*

Smears of the Prevertebral Green Tissue. Smears stained with hematoxylin and eosin, Wright's method, and the triacid show that the cells are chiefly of the "large lymphocyte" type as found in the blood of this case. The majority have no protoplasmic rim. Many show eosinophile granulation. Clumped and fragmented forms are numerous and many of the nuclei are vacuolated. Few red blood cells are found in the smears.

Green Tissue from Sternum. The microscopic study of this shows precisely the same structure and character of infiltration of the periosteum and overlying fat and connective tissues as in the case of the prevertebral green tissue. If there is any difference the number of eosinophiles is greater. Smears from this tissue show the same "large lymphocyte" type of cell, the majority being eosinophilous.

Bone-marrow. Sections of the sternal marrow show that the normal marrow elements are almost wholly replaced by cells of the same type as those of the periosteal infiltration—that is, by cells of the large lymphocyte type, the majority showing eosinophile granulation. No bone-marrow giant cells are seen. Very few red blood cells are present and only two cells were found that could be regarded as nucleated red cells. Few neutrophile myelocytes are present and small lymphocytes and polymorphonuclears are also very few in number. Transition forms between the large lymphocytes with small protoplasmic rim and those with more abundant protoplasm containing eosinophile granules are numerous. Inasmuch as the eosinophile "large lymphocyte" passes by transition forms into cells morphologically identical with eosinophile myelocytes, this fact may be taken as evidence of the derivation of the latter type of cell from the former. The eosinophiles are somewhat unevenly distributed; in some fields 50 to 80 per cent. of all nucleated cells may show eosinophile granulation, in others the proportion may drop to 10 to 20 per cent., but in many sections the majority of fields show a preponderance of eosinophiles. The polymorphonuclear eosinophiles are relatively very few. The nuclei of the majority of the eosinophiles in general resemble those of the non-eosinophile large lymphocytes. All possible transition forms exist between such eosinophiles and those forms with more abundant protoplasm resembling eosinophile myelocytes. In their general characteristics, size, shape, pale nuclei, small amount of protoplasm, etc., the cells constituting the mass of the sternal marrow are identical with those of the periosteal infiltration. The capillaries and bloodvessels of the mar-

row are nearly completely obturated by cords and masses of cells of the same type. The delicate reticulum of the marrow appears to be but slightly increased.

Smears of Sternal Marrow. Smears of the sternal marrow fixed in absolute alcohol and ether and stained with hematoxylin and eosin, triacid, etc., or fixed and stained by Wright's method are composed almost wholly of cells of the "large lymphocyte" type, the majority containing eosinophile granules. Numerous large eosinophile cells with very pale, large, single nuclei are also present. These resemble eosinophile myelocytes; many of the nuclei are vacuolated. There is a great variation in the size of the eosinophiles, and numerous transition forms exist. The majority of the non-eosinophiles have little or no protoplasmic rim and correspond with the cells found in the periosteal infiltration and in the bloodvessels. The nuclei of these also show vacuoles of varying size. Numerous degeneration forms are present. The smears contain but few red blood cells and only a very few nucleated reds. The background of the smears is made up to a very large extent of free eosinophile granules.

Vertebral Marrow. Sections of decalcified portions of the bodies of the vertebræ show an enlargement of the marrow spaces and a rarefaction of the bony trabeculæ. The enlarged marrow spaces are filled with closely crowded cells of the "large lymphocyte" type identical with those found in the sternal marrow, prevertebral and sternal periosteal infiltrations and in the bloodvessels. The number of cells having a rim of protoplasm is somewhat greater than elsewhere, and many cells show a distinct cell body. There are also more degenerating forms. The eosinophile cells are not quite so numerous as in the sternal marrow or the periosteal infiltrations, but nevertheless in the majority of fields form a relatively high proportion of all cells present. In the portions fixed in Müller's fluid the protoplasm of the majority of the cells replacing the marrow elements is distinctly chromaffinic to some extent, having a distinct brownish or greenish-yellow color. There are but few red cells and no nucleated red cells were found. The polymorphonuclears and small lymphocytes are relatively very rare. No bone-marrow giant cells were seen and no plasma or mast-cells found. Owing to the fixation used the neutrophile cells could not be distinguished. In some of the large lymphocyte forms having an abundant protoplasm very small and light eosinophile granules are present. The reticulum of the marrow is apparently slightly increased and consists of fine fibrillæ.

The most important fact determined in regard to the relationship between the marrow condition and the prevertebral infiltration is the demonstration of the direct connection existing between the two. Sections made through the prevertebral green tissue and periosteum and extending into the body of the vertebra show that the large masses of cells in the enlarged marrow spaces are in many instances directly continuous with the periosteal infiltration by means of relatively large openings in the bone. Smaller cords of cells extend from the marrow spaces through small openings in the bone and are continuous without break with the periosteal infiltration. Such direct continuity between the mar-

row spaces and the periosteal infiltration are so numerous that they can be seen in nearly every section. The openings are most probably enlarged lymphatics or bloodvessels. Red cells occur in some of them in association with the cells of the large lymphocyte type. In other cases the growth of cells in the medullary spaces appear to have caused a disappearance of bone and a direct extension of cell growth outward into the prevertebral tissues. The infiltration from the vertebræ does not extend into the intervertebral disks and is scanty over them. It surrounds the body of the vertebra more or less uniformly, but is most marked at those places where it is continuous with the growth in the marrow spaces. In some places masses of cells have grown or collected beneath the periosteum, raising it from the bone. The various pictures presented suggest growth outward from the bone and not from without into it. The spinal nerves and ganglia are surrounded by the infiltration and are to some extent themselves infiltrated. There is an increase of interstitial connective tissue within some of the ganglia.

The careful study of such sections leads to the conviction that we have to deal here with a *primary growth within the marrow spaces which infiltrates or grows directly through the lymphatics and bloodvessels or breaks through the bone and secondarily involves the periosteum and surrounding tissues.* The cells of this growth are identical morphologically with the so-called large "lymphocytes," large mononuclears, and eosinophile myelocytes of the normal bone-marrow.

Smears of Vertebral Marrow. Smears of the vertebral marrow fixed in absolute alcohol and ether and stained with hematoxylin and eosin, triacid, etc., or fixed and stained with Wright's, present the same picture as those obtained from the sternal marrow. Few red cells are present, and no nucleated forms were found. The number of eosinophiles appears not so great, and there is a larger proportion of degenerating forms. The majority of the nuclei have either large or small vacuoles, many nuclei consisting of a large vacuole having only a faint rim of chromatin. Numerous nuclear forms suggesting clumped mitoses are present as well as those forms suggesting amitotic division. The background of the smears is made up chiefly of eosinophile granules. Numerous very pale nuclei covered with eosinophile granules and having no protoplasmic body are seen.

Marrow from Tibia. Sections show a fatty marrow containing small, irregular islands of tissue exactly like that of the sternal and vertebral marrow, consisting of cells of the "large lymphocyte" type with a high proportion of mononuclear eosinophile cells of varying size and shape. In such islands the normal marrow tissue is entirely replaced. They contain but few red blood cells, and nucleated red cells are extremely rare. From these islands irregular cords of similar cells extend outward through the distended capillaries and blood spaces between the fat cells, the cords becoming smaller as the distance from the main island increases. The appearance is that of a growth extending from a center out into the neighboring tisssue through blood and lymph spaces. This growth is not at all uniform and in many of the capillaries between the fat cells the dilated

lumen may be packed with red cells, few cells of the lymphocyte type being present. In such blood spaces nucleated red cells are occasionally seen, and a few bone-marrow giant cells are also found. Neutrophile myelocytes are more numerous and the polymorphonuclears and small lymphocytes are also more common than elsewhere. Portions of the fatty marrow appear fairly normal with small collections of apparently normal red marrow, but even here the prevailing type of cell is the large lymphocyte. Eosinophiles are not so numerous in these areas.

Smears of the marrow from the tibia show more red blood cells and fewer eosinophiles than the smears of the sternal or vertebral marrow. The red cells are pale and show a greater or less irregularity of size and shape. Nucleated reds are less rare. The prevailing type of cell is, however, the "large lymphocyte." Few of these have any protoplasm, and the majority of the nuclei contain vacuoles. The background contains many free eosinophile granules.

Spleen. Sections show a diffuse hyperplasia, both cellular and reticular. The distance between the trabeculæ is increased. The follicles are almost entirely absent, being represented only by scattered small collections of lymphoid cells around some of the small arteries and the trabeculæ. The increase in the fine reticulum of the pulp is well marked; the blood spaces are obliterated or contain few or no red cells. The spaces of the reticulum are filled with cells that are chiefly of the large lymphocyte type, a very large proportion being eosinophiles. In many fields the number of eosinophiles is greater than the non-eosinophiles. Many neutrophile myelocytes are also present and the number of polymorphonuclears and small lymphocytes is greater than in the bone-marrow. On the whole, the pulp presents a distinctly myeloid character except for the absence of red cells and giant cells. The small follicles are made up almost wholly of small lymphocytes and contain very few eosinophiles or none at all. There is no infiltration of eosinophiles or of other cells in the connective tissue of the trabeculæ; as a rule the eosinophiles stop sharply around the border of both follicles and trabeculæ. A very striking feature of the sections of the spleen is the fact that while the splenic arteries are empty or contain many cells of the large lymphocyte type, the veins are distended with red blood cells with a relatively small number of white cells. Of the latter the polymorphonuclears and cells of the lymphocyte type are in preponderance.

Lymph Glands. In general the sections of the lymph glands present a cellular hyperplasia, large numbers of cells of the "large lymphocyte" type infiltrating the lymphoid tissue and replacing to some extent the cells of the latter. The degree of infiltration varies in different glands. In some the "large lymphocytes" are found chiefly in the sinuses and in the medullary cords. Germinal centers are rare. Eosinophile cells are found in large numbers in association with the "large lymphocytes." They are chiefly mononuclear and resemble the eosinophile cells found in the bone-marrow and the periosteal infiltrations. They are also present in large numbers in the connective-tissue trabeculæ, par-

ticularly near the hilum of the glands. The number of eosinophiles varies, however, in different glands. In the case of the glands taken from the thymus region the cellular infiltration is very marked. In the greenish gland from this region the lymphoid cells are to a large extent replaced by large lymphocytes, the trabeculæ are farther apart than normally, and the sinuses are wholly or partly obliterated. No germ centers were found in it. In the lymph sinuses of the majority of the glands there is a distinct proliferation of both the endothelium and the reticulum, the reticular spaces being filled with large endothelial cells, "large lymphocytes," and eosinophiles. Numerous degenerating cells are seen. The same appearances suggesting both amitotic and mitotic division are found here as in the periosteal infiltrations and the bone-marrow. In the majority of sections there is no evidence of an infiltration of the capsule or of the tissues about the gland. In some instances, however, there is an infiltration of cells of the "large lymphocyte" type extending through the capsule and into the surrounding adipose tissue. Such infiltrations are not as a rule marked, but bear in general the same character as those found elsewhere.

Hemolymph Nodes. In the hemolymph nodes from the retroperitoneal region there is a similar diffuse cellular hyperplasia or infiltration of cells of the same type. Germinal centers are absent; the lymphoid tissue is replaced to a greater extent by myeloid tissue of the same nature as that found in the spleen. Numerous mononuclear eosinophiles are present, and great numbers of these occur also in the sinuses and in the connective tissue of the trabeculæ and capsule. The blood sinuses are nearly obliterated and contain but few red cells; there is a reticular and endothelial proliferation, in the meshes of which lie "large lymphocytes," mononuclear eosinophiles, endothelial cells, etc. Phagocytes containing red cells and pigment are fairly numerous in some nodes, but on the whole are greatly diminished. Neutrophile myelocytes are occasionally found, and a few giant cells with large, deeply stained, knobbed nuclei resembling those of the bone-marrow were also seen. In some nodes the greater part of the lymphoid tissue is replaced by a cellular tissue, resembling in all respects that of the sternal and vertebral marrow and the periosteal infiltrations. Such new-formations are analogous to metastases, the surrounding tissues being somewhat compressed and infiltrated. The general picture is that of a gradual replacement of the tissues of the lymph node by the new atypical "lymphocyte" tissue. As a rule such proliferations appear to begin in the sinuses and not in the lymphoid follicles or germinal centers, the latter being latest involved. In those nodes showing such proliferations the atypical cells of the peripheral sinus infiltrate the capsule and pass beyond it into the surrounding adipose tissue. Such extensions beyond the capsule are not in any case marked. Large numbers of eosinophiles occur in the infiltration of the capsule and the adipose tissue. A large proportion of the cells replacing the lymphoid tissue consists also of eosinophile cells. In some nodes the number of eosinophiles is very great. Numerous degenerating lymphocytes are also present. In all of the hemolymph

nodes the large lymphocyte cells are most numerous in the blood sinuses. The picture presented is that of a proliferation of these cells beginning in the sinuses and not in the lymphoid tissue.

Lungs. The sections of the lungs present small areas of emphysema and atelectasis, but the alveoli in general are in a state of moderate distention. Anthracosis is slight or moderate. The larger vessels are distended and filled with white cells, the great majority of which are mononuclear and of the large lymphocyte type. They are of the same variety as those seen in the periosteal infiltrations, bone-marrow, spleen, etc. Eosinophiles are not so numerous as elsewhere; in some vessels but very few are found. As a rule the arteries are more distended with cells than are the veins. The capillaries of the alveolar walls are likewise distended and filled with cells, the majority of which are large mononuclears or large lymphocytes. The general appearance of the sections is that of a leukemic lung. Scattered everywhere throughout the lung are small groups of islands of closely crowded cells, the majority being mononuclears of the "large lymphocyte" type. While many of these islands are in the immediate neighborhood of the large vessels, and undoubtedly in some cases occupy the site of the peribronchial lymph nodes, the majority show no such relations. There are all possible transition stages between very small collections of cells lying upon the alveolar walls to larger masses filling several alveoli. In these larger masses the alveolar walls directly involved are ruptured or destroyed, the collection of cells filling up and distending several alveoli. Mononuclear eosinophiles are numerous in these masses, but occur to a less extent than in the other regions described above. The majority of the masses consist apparently of free cells; no reticulum can be made out. In some cases the outlines of the alveolar walls included in these cell masses are wholly lost, and there is apparently some fibroblastic proliferation extending into the group of cells, giving it something of a reticulum. The alveolar spaces about many of these small masses contain blood, sometimes also fibrin, and desquamated epithelium. In other parts there are collections of cells containing more polymorphonuclear forms and surrounded by areas of edema and hemorrhage. In these areas the smaller bronchi are filled with cells, the majority being polymorphonuclear. It is evident that such areas are to be interpreted as foci of bronchopneumonia. In the pleura there are present very small groups of mononuclear cells, filling distended capillaries and infiltrating somewhat the neighboring tissues. In general the picture presented by the lung is that of a leukemic condition with infiltrations of cells which are proliferating after the manner of tumor cells.

Heart. This was preserved as a museum specimen by distending and hardening whole. No microscopic examination has yet been made.

Liver. Many sections present the appearance of a leukemic liver, the intralobular capillaries being filled with cells, and the islands of Glisson's capsule in many places showing a cellular infiltration. These changes, however, vary greatly in degree in different parts of the organ. As a rule the liver lobules are

somewhat smaller than normal, and the islands of Glisson's capsule relatively increased. There is no actual increase of connective tissue except in certain areas where the infiltrated capsule shows also a fibroblastic hyperplasia. The liver cords are atrophic in some areas, and the intralobular capillaries distended, and in many places crowded with cells of the "large lymphocyte" type. The central veins are dilated and in some instances also contain masses of similar cells. In the cells of the central zone of the liver lobule there is an abundant, yellowish-brown, granular pigment which does not give the iron reaction (hematoidin). The cells of the peripheral zone contain a moderate amount of brown, finely granular pigment which does give the iron reaction (hemosiderin). In some lobules fat drops are also present in the cells of the peripheral zone. The liver cells on the whole show a slight degree of fatty degeneration. While some islands of Glisson's capsule show a marked cellular infiltration, others show little or none. The cells of the infiltration are of the type of the "large lymphocyte," and in the majority of cases have eosinophile granules. In some islands nearly every cell is an eosinophile. In the more densely infiltrated islands evidences of enlargement or growth are shown by the compression and condensation of the liver cells immediately about the island. The impression is gained of an infiltration in which the cells are proliferating. Smaller masses of cells consisting in many cases chiefly of eosinophiles are also found scattered throughout the liver lobules. These apparently consist of collections of the atypical lymphocyte cells in the dilated capillary, with their further proliferation, and the resulting compression of the neighboring liver cells. Evidences of such pressure condensation and atrophy are clearly seen. In the larger of these masses some reticular proliferation is also seen. In some portions of the sections the collections of cells in the capillaries is so great that the latter appears as cords of deeply staining cells, while the columns of liver cells are in a condition of marked fatty degeneration or simple necrosis, staining a very pale pink or a deep red, the liver-cell nuclei being wholly lost. In these areas there are great numbers of degenerating lymphocytes in the capillaries. Relatively few eosinophiles are seen in the distended capillaries. In many capillaries there is present also a well-marked endothelial proliferation. It is to be noted also that the number of eosinophiles in the large vessels of the liver is relatively much less than in the infiltration in Glisson's capsule, or in the larger collection of cells in the lobules. In interpretation of the liver changes the condition may be regarded as due to the presence in the bloodvessels of the liver of cells having the power to proliferate both in the vessels and after passing out into the connective tissue. The process is therefore analogous to tumor metastasis and infiltration.

Pancreas. Sections show slight atrophy of the lobules, fatty infiltration of the interlobular connective tissue, and beginning postmortem change. Many cells of the "large lymphocyte" type are present in the capillaries and small arterioles. No infiltration of the connective tissue was seen.

Stomach. There is a moderate chronic atrophic gastritis with excess of mucous formation in the glands. The interstitial tissue is somewhat increased and

presents numerous small collections of cells which are chiefly mononuclear, many being eosinophile. These small collections of cells bear no especial relations to the lymphoid follicles. The latter are somewhat hyperplastic and contain an increased number of cells of the "large lymphocyte" type. Numerous eosinophiles are present in the follicles and also in the small groups of cells. The small tumor from the fundus consists of bundles of unstriped muscle and fibrous connective tissue running in irregular whorls (leiomyofibroma).

Intestine. Catarrhal enteritis. The bloodvessels of the intestinal wall are collapsed and empty for the greater part. Some contain masses or cords of cells of the "large lymphocyte" type. In the mucosa and submucosa there are very small collections of mononuclear cells, many of which are eosinophile. In one instance a larger mass of similar cells was found in the muscularis, small cords of cells extending from the main mass and infiltrating the surrounding muscle. The peritoneal surface is in many places covered with a layer of free cells, mostly of the "large lymphocyte" type, and containing many eosinophiles. The appearance is not that of an inflammatory exudate. The cells are clumped together in irregular groups, and probably represent free cells of the peritoneal cavity.

Kidneys. There is slight atrophy, the glomeruli in the majority of fields being more numerous than under normal conditions. The cells of the convoluted tubules show a slight degree of cloudy swelling. The bloodvessels of the medullary pyramids are dilated; many are filled with red blood cells with relatively few leukocytes; others are completely filled with cords or masses of cells of the "large lymphocyte" type. In these masses numerous eosinophiles are present. In the bloodvessels of the cortex there is a similar distribution of cells. Throughout the cortex there are numerous collections of cells replacing the kidney structure, the largest being 2 to 5 mm. in diameter. They are situated chiefly just beneath the capsule, which is thickened and infiltrated with cells of the same kind. From the main mass of cells irregular cords infiltrate the surrounding kidney tissue following the intertubular connective tissue. In the central portions of these masses all trace of kidney structure may be lost; occasionally an atrophic glomerulus or remains of tubules may be present. There is a distinct new-formation of reticulum, and in some cases there is a picture of an interstitial nephritis immediately about the cell mass. About many of the latter, however, the kidney shows no recognizable changes. In others the tubules and glomeruli of the surrounding infiltrated zone are atrophic or compressed or even necrotic. The cells of these masses are almost wholly mononuclears of the type of large lymphocytes, many being eosinophiles. In some cases nearly all of the cells are mononuclear eosinophiles. The cells of the surrounding infiltration are of the same type. While numerous individual degenerating cells are found, there is no degeneration *en masse* of any portion of these cellular foci. Smaller cell groups are also found throughout the cortex, usually in the immediate neighborhood of a capillary or arteriole filled with white cells. Some of the smaller groups consist wholly of mononuclear eosinophiles. Even in

these smaller collections there is a well-marked proliferation of the kidney reticulum. The general picture presented microscopically is that of metastatic growth of cells of the large lymphocyte type, replacing the kidney tissues by means of a slow infiltrative proliferation.

Bladder. Chronic cystitis. Thickening of mucosa and submucosa. Increase of leukocytes in many bloodvessels, the cells being chiefly mononuclear and of the "large lymphocyte" type. No infiltration found.

Prostate. Collections of mononuclear cells of "large lymphocyte" type in some of the bloodvessels. About these there is a limited infiltration, in many cases containing many eosinophiles.

Testis. Similar collections of cells are found in some of the bloodvessels and similar small infiltrations near them. The lining epithelial cells show an unusual degree of pigmentation.

Spinal Cord. There is some evidence of atrophy and degeneration. (A more complete study of the changes in the cord has been left for another time.) There is no cellular infiltration of cord or meninges. An increased number of leukocytes, chiefly mononuclear, is found in many of the smaller vessels.

Bloodvessels. The bloodvessels throughout the entire body contain an excess of white cells, the majority being mononuclear cells of the "large lymphocyte" type. The number of cells in the vessels differs greatly in different parts. In many places the distention of the lumen, the packing of the cells, and the infiltration of the vessel wall convey the impression of an intravascular proliferation. The proportion of eosinophiles is much less in the vessels than in the tissues.

Pathologic Discussion. Summing up the most important histologic changes as shown by the microscopic study of this case, the primary condition appears to be a tumor-like hyperplasia of the red marrow of the vertebræ and sternum with secondary infiltration of the periosteum and neighboring structures, and the occurrence of metastasis-like infiltrations and nodules in the lungs, liver, kidneys, hemolymph nodes, tibial marrow, etc., associated with a cellular hyperplasia of spleen and lymph glands, and evidences of cell proliferation within the smaller bloodvessels in various parts of the body.

That the changes in the marrow of the vertebræ and sternum are primary is shown by the fact that the normal marrow elements are completely replaced by the new cells, the marrow spaces enlarged, and the bony trabeculæ rarefied, and by the direct extension of the cell growth in the marrow spaces outward from the bone beneath and into the periosteum. The prevertebral chloromatous tissue is, therefore, nothing more than the periosteum, prevertebral fat-tissue, and fascia infiltrated secondarily by cells coming from the bone-marrow through the blood and lymph vessels, and by direct extension through openings in the bone. The chloromatous tissue over the sternum is similarly interpreted. The greater extent and larger mass of the green tissue along the vertebræ, together with the greater changes in the vertebral marrow spaces and trabeculæ, would indicate that the vertebral condition antedated the sternal.

The cells of the tumor-like hyperplasia of the marrow correspond in their morphologic and staining characteristics to two classes of cells found normally in the bone-marrow, viz., cells of the type variously known as the *large lymphocytes, undifferentiated lymphocytes, large mononuclears*, etc., and cells of the *myelocyte type*, both eosinophile and neutrophile, the eosinophile forms greatly predominating. In general it may be said that about half of the new cells fall into the class of "large lymphocytes" and about half into that of the eosinophile myelocyte. Between the two all possible transition forms exist, and these may be classed with that type which they most resemble. From the character of the transition forms found the evidence is strong that the cells of the myelocyte type are derived from those of the "large lymphocyte" type. This supports the view of Ehrlich and others held as to the origin of the myelocytes in the normal marrow.

The condition of the vertebral and sternal marrow may therefore be interpreted as a hyperplasia of the cells of the "large lymphocyte" type or of their parent cells, a part of the new "large lymphocytes" resulting from this proliferation becoming transformed into myelocytes according to their ordinary course of development under normal conditions. The atypical character of the new "large lymphocytes" and myelocytes produced by this abnormal proliferation may be taken as evidence of the neoplastic nature of the process. This is shown particularly in the loss of the normal differentiation into normal neutrophile and eosinophile myelocytes. In so far as the vertebral and sternal marrow are concerned we have to deal therefore with *a hyperplasia of the large lymphocytes which replaces the other elements of the marrow and in the extent and manner of its growth assumes the character of a neoplasia.*

The neoplastic character of the marrow hyperplasia is further shown by the changes in the walls of the marrow spaces, the infiltration through the blood and lymph vessels, and the direct extension from the bone into the tissues of the periosteum and other neighboring structures. The cells of this infiltration are precisely identical with those of the marrow spaces; there is, therefore, an infiltration of the periosteum and prevertebral tissues with cells of the "large lymphocyte" and myelocyte types, this infiltration being distinctly neoplastic in character. The infiltrating cells are proliferating in the tissue spaces, and are destroyed and replacing the tissues infiltrated. Such destruction is not of a very rapid or malignant type; the infiltrated tissues show but slight reaction, there is some connective-tissue increase, the walls of many vessels are thickened, and in some of the smaller vessels there is an endothelial hyperplasia. Nerve trunks and ganglia show a more or less decided atrophy, striped muscle fibers show all stages of atrophy, and the fat cells of the infiltrated prevertebral adipose tissue also present various stages of pressure atrophy. About the nodular masses of the infiltration the tissues often show some degree of condensation and pressure atrophy. Aside from the purely mechanical effects, pressure and blocking of vessels, etc., the disturbance of the tissues infiltrated is remarkably slight. The

growth of the cells through the tissues appears to be largely the result of a direct proliferation in the bloodvessels and lymphvessels, the cells growing through the vessel walls, of proliferating in the tissue spaces after having passed out from the vessels. The slight effects upon the tissues may be explained by the assumption of a relatively slight antagonism between the body tissues and the new cells. In general the new cells of the infiltration may be regarded as free cells proliferating in the tissue spaces. Even in the larger and denser masses of the prevertebral region the reticulum is apparently the original reticulum of the tissue more or less thickened, and there is no new-formation of bloodvessels. The antagonism between the new-growth and the tissue cells must therefore be much less than in the case of the infiltrating tumors, carcinoma, and sarcoma.

From the microscopic appearances the proliferation of the new cells is chiefly by amitotic division. The numerous indentation and constriction forms of the nuclei, the double nuclei, etc., are taken as supporting this view. Division and growth of the cells within the bloodvessels undoubtedly takes place. Throughout the body dilated vessels filled with masses of the new cells were found; in many of these the vessel walls are infiltrated or grown through with cells, and about the vessel there is a more or less well-marked infiltration. Evidences of proliferation within the lumen of the bloodvessels are especially well marked in the liver.

The nodules in the lungs, liver, kidneys, hemolymph nodes and tibial marrow appear to be true metastases arising chiefly through the intravascular proliferation of cells and the secondary invasion of the surrounding tissue. As in the prevertebral infiltration, the metastatic nodules have but little antagonistic action upon the tissues at the site of the growth; there is but little reaction and but little new-formation of reticulum and apparently no new-formation of bloodvessels. In the kidney alone is the increase of reticulum at all pronounced; in this organ the secondary nodules are in many cases the seat of an interstitial change suggesting a chronic nephritis. In general the effect of the metastases upon the surrounding tissues is chiefly a simple atrophy. In the liver there is also some fatty degeneration and occasionally a localized necrosis about the cell masses. The cells composing the metastases are identical with those of the sternal and vertebral marrow and the periosteal infiltrations.

The bloodvessels throughout the entire body show an increase in the number of white cells, the picture presented being that of a marked leukocytosis or leukemia. The greater part of these white cells in the vessels is found to be identical with the "large lymphocytes" of the primary marrow growth, the prevertebral infiltration, and the metastases. As mentioned above, there are evidences of the intravascular proliferation of these cells. The case therefore presents the picture of *a leukemia of the large lymphocyte type associated with a primary neoplastic hyperplasia of the bone-marrow, chloromatous infiltrations of the periosteum and metastases in various organs. That the leukemia is secondary to and dependent upon the marrow condition there can be no doubt.*

Assuming that the process is essentially neoplastic in its character, it is evident that the new-growth is not identical with any of the known neoplasms. The terms lymphoma, lymphosarcoma, myeloma, etc., cannot be appropriately applied to it, nor is it satisfactory to class it simply as sarcoma. The individual character of its cells and its manner of growth give it a unique place as a neoplasm, and it must fall into a class of its own—a class to which probably all the leukemias belong—due to an abnormal proliferation of the parent cells of the white cells of the blood. To such tumors the term *myeloblastoma* or *leukoblastoma* might be applied, but a discussion of the propriety of such designations will be reserved for another time.

White accepting the neoplastic character of this case of chloroma, the fact remains that nothing is disclosed as to the etiology of such an abnormal hyperplasia of the bone-marrow elements. Intoxication or infection is not ruled out as the etiologic factor, and we are in exactly the same position here as we are in regard to the question of the etiology of neoplasms in general. Pending the discovery of the ultimate nature and cause of such hyperplastic proliferations, they may with propriety be classed temporarily with the neoplasms.

It is quite evident in this case that there is no picture of a general disease of the lymphoid tissues of the body, as in certain cases of lymphosarcoma, etc. The changes in the spleen and lymph glands are purely secondary. The germinal centers in these show no signs of excessive proliferation; on the other hand, they are involved last of all. The metastases do not necessarily occupy the site of the lymphoid tissue of the organs in which they are found; but their location is determined independently by proliferating collections of cells in the blood-vessels. This is shown particularly clearly in the lungs, stomach, and intestine, where the lymphoid nodes themselves are but little involved, while numerous small collections of cells are found along the arterioles. *The idea of a general lymphatic affection may be rejected here; the process is myelogenous in origin and has become generalized through the bloodvessels. It is a general disease only in the sense that the bloodvessels contain cells having the power to proliferate intravascularly and to set up infiltrations and metastases.*

The general myeloid character of the spleen and some of the hemolymph nodes may possibly be due to some effort at compensation for the lost marrow function. As a result of the replacement of the normal red marrow by the atypical lymphocyte and myelocyte tissue the formation of the red blood cells must have been greatly diminished. The extreme anemia shown by the patient is thereby explained. No evidence exists of any marked hemolysis. The pigment of the liver may be explained by the lessened splenic and hemolymphatic functions, although it is probable that the changed conditions of the blood plasma may have caused some direct hemolysis. The large numbers of individual degenerating large lymphocytes found everywhere may have given rise to some intoxication. It is very probable that the extreme anemia, either with or without the co-operation of these more doubtful factors, would explain the majority of

the clinical symptoms. The involvement of the spinal nerves and ganglia by the infiltrations is also a very important factor in the explanation of the symptomatology. The eye and ear conditions might be similarly explained, though the anemia itself might account for both. The changes in the blood would explain the petechial hemorrhages and the endothelial proliferation. It may be well, however, to repeat here that the primary process—the atypical proliferation of the marrow cells—may be due to an intoxication having a marked myelotoxic action. Of such an intoxication we have no proof.

As to the nature of the green color of the bone-marrow and periosteal growths the case offers no explanation. No evidences of pigment were found in the cells, and no fatty bodies reacting with Sudan III. or with osmic acid. The guaiac test was not employed. Hydrogen peroxid and ammonium hydroxid were not used upon the fresh tissue and had no effect upon the fixed material. The supposition that the color might be due to the large number of eosinophiles present would not be supported by other cases of chloroma in which it is definitely stated that few eosinophiles were present. The best explanation of the color would appear to be that it is a true parenchymatous color.

Charcot-Leyden crystals were not observed in this case.

From the above study and discussion the following diagnosis is obtained:

Pathologic Diagnosis. Chloroma (primary hyperplasia of the "large lymphocytes" of the red marrow); secondary chloromatous infiltrations of the prevertebral and sternal periosteum; metastases in lungs, liver, kidneys, hemolymph glands, bone-marrow, etc.; secondary hyperplasia of spleen and lymph glands of thymus region; leukemia (large lymphocyte type); severe anemia; general atrophy and parenchymatous degeneration; chronic atrophic gastritis; lipomata of shoulders; myofibroma of stomach wall.

EPICRISIS. According to the commonly accepted definition at the present time chloroma is a "tumor belonging to the general class of sarcoma, more precisely to the group of lymphoma, lymphosarcoma, so-called leukemic and pseudoleukemic tumors, etc., characterized by its green color and arising primarily in the periosteum, particularly in that of the cranium." The study of the present case as given above shows that this definition must be changed essentially, and that based upon our case a new conception of the nature of chloroma may be formed. In this case, at least, chloroma is a primary tumor-like hyperplasia of certain elements of the bone-marrow; the periosteal condition is purely secondary, and the character of the neoplasia does not warrant its classification as a lymphoma, lymphosarcoma, or simple sarcoma, but assigns it to a class of its own, a class of neoplastic hyperplasias arising from the atypical proliferation of the parent-cells of the white blood

cells, hence belonging to the leukemias. Chloroma could therefore be primary in any part of the body in which white blood cells are formed, either under normal or abnormal conditions. From the reported cases of this condition it would appear, however, that the cells proliferating in chloroma are those that produce the large lymphocytes and their descendants and not those giving rise to the small lymphocytes. In addition, the constant localization of the green growths in association with the bones containing red marrow supports the view that chloroma is essentially myelogenous, and the existence of a primary chloroma of the spleen or lymph nodes remains to be demonstrated.

Of the previous writers upon chloroma Guembel appears to be the first to regard the affection as a primary bone-marrow disease. The recently reported case of Klein and Steinhaus (see above) is, however, a striking confirmation of the findings in our case and of our deductions. In their case the newly formed cells bear the character of neutrophile myelocytes, and represent a higher differentiation than in our own case, in which the cells are about half large lymphocytes and half mononuclear eosinophiles. It is evident, therefore, that different varieties of chloroma will exist in so far as the blood picture is concerned, just as in the case of the leukemias.

The "free" character of the cells of the chloromatous infiltrations and metastases and of the bloodvessels and tissue spaces would easily explain their disappearance under the influence of certain infections, intoxications, *x*-rays, etc., such as we know occurs in the case of leukemia. The action of such agents could be explained by the assumption of a destruction of cells exceeding or equalling their production, or by an inhibition of the proliferative activity of the parent cells, or by direct action upon the etiologic factor. The destruction of large numbers of the new cells might in itself give rise to an intoxication. Interesting questions are opened up along this line which must be solved later.

Without burdening this paper further with additional details and arguments we think we are justified in arriving at the following conclusions:

CONCLUSIONS. 1. *Chloroma is a tumor-like hyperplasia of the parent cells of the leukocytes, primary in the red marrow, the periosteum being involved only secondarily.* The possibility of a primary chloroma in any part of the body in which white cells are formed must be considered.

2. As a result of this leukoblastic hyperplasia atypical leukocytes or leukocytes corresponding to some one of the normal types may appear in the circulating blood in varying number. Chloroma is therefore to be classed with the leukemias.

3. The white cells resulting from the atypical proliferation may in different cases attain different stages of differentiation. In some cases they may be of the large lymphocyte type, in others of the type of neutrophile or eosinophile myelocytes. At different stages of differentiation atypical forms may be produced. Whether a small lymphocyte type exists remains to be more definitely shown.

4. It is evident, therefore, as in the case of other leukemias, that the blood picture in chloroma may be very varied, and if this be used for a basis of classification it is possible to designate different varieties of chloroma.

5. It is also possible that in certain cases, or possibly stages, of chloroma the hyperplasia of the parent-cells may reach such a stage that the new forms do not get into the blood stream in such numbers as to give the picture of a leukemia. An aleukemic chloroma is therefore possible.

6. The essential difference between chloroma and other forms of leukemia is the more marked neoplastic character of the former and the formation of the green infiltrations and metastases. The following classification of chloroma is therefore proposed:

- Chloroma (chloromatous leukemia)
  - 1. Aleukemic chloroma (?).
  - 2. Leukemic chloroma
    - 1. Small lymphocyte type (?).
    - 2. Large " "
    - 3. Neutrophile "
    - 4. Eosinophile "
    - 5. Atypical.
    - 6. Mixed.

7. Chloroma is probably to be regarded as a more malignant form of leukemia. The white cells resulting from the atypical proliferation have the power of multiplying in the blood streams and in the tissue spaces, thus giving rise to masses of cells having the characteristics of metastatic tumors. It is probable that the proliferative activity is proportionate to the lack of differentiation. In the neutrophile and eosinophile forms we should expect a less marked tendency to proliferation; on the other hand, the large lymphocyte and atypical forms would show a greater proliferative capacity, and hence be more malignant. The aleukemic types

theoretically would be the most malignant of all, and present characteristics more closely allying them with the sarcomata.

8. The atypical hyperplasia of certain of the elements of the bone-marrow leads to the crowding out and replacement of the erythroblastic elements, and a consequent lessening of red-cell formation. Chloroma is therefore attended by and is the cause of a severe *anemia*, to which the chief symptoms of the disease are probably due. This anemia, while it may resemble pernicious anemia in many ways, is essentially *an anemia of deficient hematopoiesis and not one of excessive hemolysis.*

9. The malignancy of chloroma depends, therefore, chiefly upon the replacement of the red marrow and the consequent diminished red-cell formation. The slight antagonism between the new cells and the body cells would otherwise place it among the relatively benign growths, except in those cases in which important nerve structures are injured by compression by the infiltrations or through rarefaction of the bones. The large numbers of degenerating white cells present throughout the body may possibly give rise to an intoxication.

10. The cause of the green color remains unknown. It is probably a parenchymatous color. It is possible that processes morphologically like chloroma may lack the characteristic green color. Such cases should be classed with the non-chloromatous leukemias.

11. While classing chloroma temporarily as a unique form of neoplasm, the question of the ultimate etiology of the process is not settled. Intoxication or infection can at present no more be ruled out than in the case of carcinoma or sarcoma. We are in the same position here as in the case of neoplasms in general.

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DISCUSSION.

DR. OSLER: I would like to ask Dr. Dock if he does not think that the clinical picture of these cases is so different from that found even in the most acute types of leukemia that this would give the best criterion for distinguishing between the two conditions.

DR. MELTZER. I would like to ask Dr. Dock whether the urine of his case was examined for the presence of Bence-Jones albumose. From Dr. Dock's description it seems that the tumors in chloroma appear chiefly on the bones of the trunk. The same localities are also the preferred seats of the swellings in myeloma. It seems also that certain conditions of the cells of the bone-marrow are to a degree common to chloroma and myeloma. It would therefore be interesting to know the condition of the urine in cases with chloroma with regard to the presence or absence of Bence-Jones body in it.

DR. DOCK: I think I must have given a wrong impression as to the severity of the cases, judging from Dr. Osler's remarks. I think he will be willing to say that in many cases of acute leukemia, especially the scorbutic cases, the picture is quite as severe as those of chloroma. Our own case was one of the most severe in its general course, and that may account for the idea I conveyed, but most of the cases give a picture like that of acute leukemia running for four or five months and ending with scorbutic symptoms.

In regard to albumose, I mentioned in my paper that by an unfortunate accident the test was not made in our case. Albumose tests have been made as a routine matter in my clinic for some time, but in this case they were overlooked. In some other cases albumose has been absent. In regard to the bones affected, of course we must remember that no case has had the bones thoroughly examined. We can rarely get permission to make a complete examination of the long bones. In this disease some of the bones have shown chloromatous marrow, but the irregularities are great; in some cases, for instance, one femur showed the chloroma and the other did not, and again the flat bones might show it while the long ones would not. As regards myeloma, I would like to ask Dr. Meltzer what kind of myeloma he refers to. Different histologic changes have been described under that name, and many cases of chloroma might be included.

ZONAL NECROSIS OF THE LIVER.

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THE liver, it is well known, is composed of lobules, or units of structure, all of which bear the same relation to the vascular system. Since blood poured into the capillary network of the lobule is collected by converging capillaries into a central vein, all parts of the lobule are not subject to the same vascular conditions, for the hepatic cells in the center of the lobule are presumably supplied with blood which is more venous in character than that which enters at the periphery.

When, for example, the liver is the seat of prolonged chronic congestion, capillaries in the center of the lobule become widely dilated and the intervening columns of cells undergo corresponding atrophy, but even with an extreme grade of chronic congestion a narrow zone of hepatic cells in the periphery of each lobule persists unchanged. Other lesions affect unequally different parts of the lobule. Rindfleisch[1] noted that amyloid substance is first deposited in a zone which, leaving the periphery of the lobule unchanged, begins midway between the center and the periphery and extends a variable distance toward the region of the central vein. He believed that this distribution was in harmony with the occurrence of amyloid degeneration in other parts of the body, since the lesion usually affects the small arteries and hence extends to their capillary system. For, he has stated, the hepatic artery penetrates half-way into the lobule and here first breaks up into a capillary network which joins the portal circulation. He has not, however, given evidence obtained from injections or otherwise to support his

[1] Text-book of Pathological Histology. Trans. 2d German ed. Philadelphia, 1872.

belief. Finding different parts of the hepatic lobule particularly susceptible to certain pathological changes, Virchow, in his lectures on cellular pathology, likewise has defined three zones in the hepatic lobule. The peripheral zone in contact with the portal vein is the chief seat of fatty metamorphosis, an intermediate zone is the seat of preference for amyloid degeneration, while the central part of the lobule is the most common seat of pigmentary infiltration.

The observation of several instances in which hyaline necrosis of the hepatic cells has been limited to a circular intermediate zone, separated by intact parenchyma both from the portal space and from the central vein, has led me to investigate the location of similar coagulative necrosis in a considereable number of cases. Such an intermediate zone has been repeatedly found to occupy a definite position within the lobule; it may be assumed that there are here peculiar conditions which make the parenchymatous cells particularly susceptible to injury.

Since the hepatic lobule is defined by the peculiar arrangement of its bloodvessels, this midzonal lesion, perhaps, is dependent upon some peculiarity of the intralobular circulation. For the present purpose it is sufficient to define the limits of the intermediate, or midzone, marked out by injury to its cells. In different instances such a zone of necrosis, though subject to slight variation, has been fairly constant in position and extent. Its outer margin has been situated from one-fifth to one-fourth the distance from the portal space to the central vein, and in width it equals approximately one-fourth the distance between these two structures. This midzone defined by necrosis marks off on the one hand a central and on the other hand a peripheral zone. The central zone, when it surrounds the transversely cut central vein, is circular in outline and occupies approximately one-half the distance to the portal space. The peripheral zone in contact with the portal space occupies from one-fifth to one-fourth the distance from portal space to central vein. The intermediate zone being circular, adjacent circles are nearest together midway between two portal spaces, and here the peripheral zones of two adjacent lobules are narrowest. (See Figs. 1 and 2.)

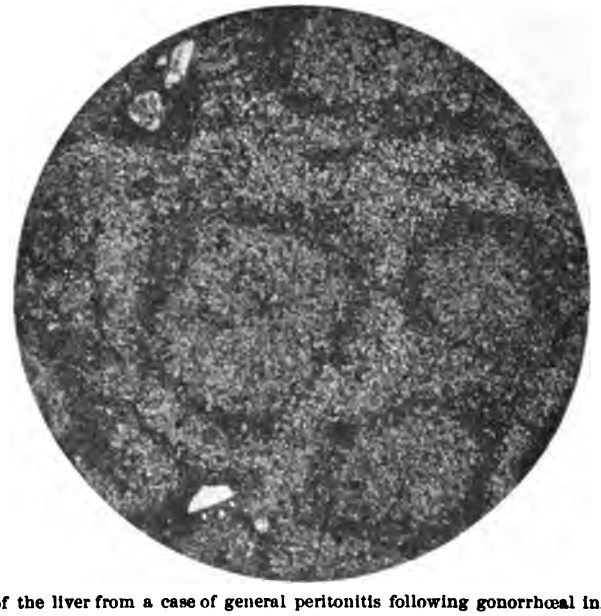
The so-called focal necroses of the liver which have been found by Jürgens,[1] Schmorl[2] and others in association with eclampsia

[1] Berliner klin. Woch., 1886.

[2] Untersuchungen über Puerperal-Eclampsie, Leipzig, 1893.

have their origin in the tissue immediately about the portal spaces. With this disease, however, the lesion does not affect the periphery of every lobule. The occasional occurrence of hyaline necrosis limited with great regularity to a peripheral zone of the lobule has been demonstrated by a case which will be described later. Hyaline necrosis, having its origin about the central vein and limited to the central part of the lobule, has been carefully described by

FIG. 1.



Section of the liver from a case of general peritonitis following gonorrhœal infection in a girl fourteen years of age, stained with eosin and hæmatoxylin; a middle zone of necrosis in each lobule stains deeply with eosin. (From a photograph taken by Dr. Charles Potter.)

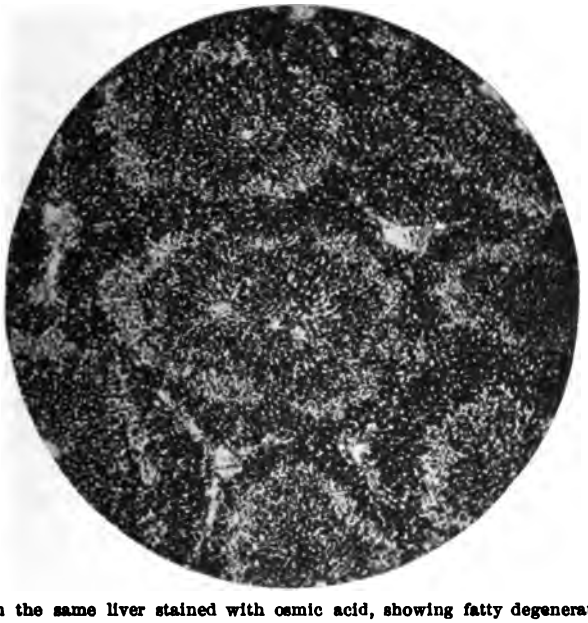
Mallory.[1] Hence each of the three zones which have been defined are individually susceptible to injurious influences.

CIRCULATION WITHIN THE HEPATIC LOBULE. Peculiarities of the intralobular hepatic circulation doubtless explain the occurrence of these zones, individually susceptible to certain lesions. The capillary network of the lobule receives blood from both the portal vein and hepatic artery, but the relation of the two vessels to one another is imperfectly understood. Rindfleisch believed that intra-

[1] Journal of Medical Research, 1901, vol. vi. p. 264.

lobular branches of the hepatic artery penetrate a short distance into the lobule and in a zone midway between the centre and periphery of the lobule form a capillary network. He did not support this view by the study of injected specimens, but, as previously mentioned, based his belief upon the distribution of amyloid degeneration. It received some confirmation from the observations of Chrzonszczewsky,[1] who injected sodium sulphindigotate and ammo-

FIG. 2.



Section from the same liver stained with osmic acid, showing fatty degeneration of the central and peripheral zones; the middle zone of necrosis is unstained.

niacal solution of carmine into the systemic veins of living animals. He reached the conclusion that the central part of the lobule is supplied with blood by the hepatic artery, while the portal vein alone supplies the peripheral part; for if before injection he ligated the portal vein, pigment was found only in the centre of the lobule, but if the hepatic artery was tied the periphery alone was pigmented. Cohnheim and Litten,[2] repeating these experiments, found that carmine injected into the jugular vein after ligation of the hepatic

[1] Virchow's Arch., 1866, Bd. xxxv. p. 153.

[2] Ibid., 1876, Bd. lxvii. p. 158.

artery is deposited exclusively in the periphery of the lobule only when an insufficient amount is employed. Pigmentation of the center of the lobule, after ligation of the portal vein, is the result of regurgitation of blood from the hepatic vein, for it occurs to the same extent if both hepatic artery and portal vein are ligated before the pigment is injected.

From a study of the liver injected after death, Kowalewsky[1] and Rattone and Mondino[2] have reached the conclusion that twigs from the hepatic artery join the capillary network in the periphery of the lobule. After the portal vein has been filled with an injected mass, material of a different color injected into the hepatic artery has been found to penetrate into a narrow peripheral zone.

The portal vein, hepatic artery and hepatic vein are in such free communication that the entire lobule can be injected from any one of these vessels. Hence artificial injections do not define the intralobular distribution of the portal and arterial blood, for doubtless differences of the venous and arterial pressures have a part in determining peculiarities of the circulation within the lobule. In order to overcome this difficulty, I have injected, through a fine needle, various substances into the hepatic artery and into the portal vein of living dogs in order that they might reach the interior of the lobules under natural conditions of arterial and venous pressure. Of especial interest in the present connection is the demonstration that the injected pigment tends to accumulate in zones situated between the center and periphery of the lobules.

Substances which penetrate with difficulty capillary vessels were injected into the hepatic artery or into the portal vein of anæsthetized animals in order to determine what part of the lobule is first reached by blood from these two vessels. For this purpose a suspension of India ink or a neutral saturated solution of ammoniacal carmine (Hoyer) was used. These substances injected into either vessel accumulate in greatest amount in the periphery of the lobule and soon completely obstruct the capillaries in this situation. From neither vessel do unbranched twigs penetrate into the lobule. The influence of the hepatic artery upon the intralobular circulation is well demonstrated by observing the effect of injection into the portal vein after ligation of the hepatic artery; when the artery has been

[1] Ref. in Schwalbe's Jahresber., quoted by Oppel, Lehrbuch der vergleichenden mikroskopischen Anatomie der Wirbeltiere, Jena, 1900, Bd iii.

[2] Arch. ital. de biol., 1889, vol. xii. p. 156

tied the injected material is limited to a narrow peripheral zone, while without ligation the pigment penetrates a greater distance, and the entire central part of the lobule is palely injected.

An ammoniacal solution of carmine prepared according to the formula of Chrzonszczewsky penetrates with great readiness the capillary vessels of the liver and soon stains the conjunctivæ and other tissues of the animal. When approximately 10 c.c. of this solution are allowed to flow from a buret through a hypodermic needle inserted into a large mesenteric vein, in well-injected parts of the liver, capillaries in contact with the portal spaces are lightly injected and carmine has accumulated in a narrow zone approximately midway between the portal spaces and the central veins of the lobules. Frequently this zone forms a band, encircling the portal space, while parts of several such irregular circles in turn surround the central vein. If the same solution is injected into the portal vein after ligation of the hepatic artery, carmine is most abundant in the peripheral part of the lobule, thus demonstrating that the occurrence of the intermediate zone is dependent upon the activity of the arterial circulation.

When, moreover, the ammoniacal solution of carmine is injected through a fine needle into the hepatic artery, or, more conveniently, into the cœliac axis, a somewhat narrow zone in contact with each portal space remains almost uninjected; but as the central vein is approached an intermediate zone of deep injection follows and is succeeded by a less deeply injected area about the central vein. In parts of the liver the injected mass apparently obstructs the hapatic artery, so that the extreme periphery of each lobule is injected, while the greater central part is wholly unpigmented.

The foregoing experiments demonstrate that both the hepatic artery and portal vein pour their blood into the periphery of the lobule, and here the influence of the arterial blood pressure is most strongly felt. When foreign material reaches the liver by the portal vein it is washed from the peripheral zone by the arterial blood and tends to be deposited in a middle zone, where the influence of the opposing circulation is less strongly felt. Hence it is not improbable that toxic substances capable of causing necrosis of the hepatic cells, brought to the liver by the portal vein, might first exert their effect upon cells within a midlobular zone. The periphery of the lobule, moreover, is supplied with arterial blood and is perhaps for this reason less susceptible to injurious agencies. The experi-

mental injections offer a probable explanation of the remarkable midzonal lesion. They do not explain the occurrence of necrosis limited to the central or to the peripheral zones of the lobule.

Zonal Necrosis of the Liver. Necrosis of hepatic cells occurring in minute scattered areas has been observed in association with a variety of infectious diseases; with malarial fever by Guarnieri,[1] with typhoid fever by Reed,[2] and with diphtheria by Barbacci.[3] Under the designation "Les taches blanches du foie infectieux," Hanot[4] has described small foci of variable size occurring most frequently upon the convex surface of the liver. They have been found, he says, with pneumonia, cholera, diphtheria, suppurative meningitis, gangrenous phlegmon, typhoid fever, variola, scarlet fever and other diseases. In his monograph upon the pathology of toxalbumin intoxications, Flexner[5] has described foci of hyaline necrosis affecting the hepatic cells in individuals dead with infection caused by the common pyogenic cocci and has pointed out their resemblance to the experimental lesions caused by poisoning with certain substances derived from the vegetable kingdom, namely, ricin and abrin, and to lesions caused by the injection of diphtheria toxin. Such substances, he believes, act directly upon the hepatic cells, causing their destruction.

Necrotic foci in which the hepatic cells have become hyaline, occurring with diphtheria, typhoid fever, or malaria, are usually of small size and occupy no definite position within the lobule of the liver. It has been difficult to explain the limitation of the lesion to a small group of cells which apparently do not differ from those nearby. Mallory has offered an explanation of the focal character of the typhoid necroses. He maintains that the large phagocytic cells, which in this disease are abundant in the spleen, finding their way in considerable number to the liver act as emboli and plug the capillary vessels, nourishing circumscribed areas. Boxmeyer,[6] studying the hepatic foci of necrosis caused by experimental inoculation with the bacillus of hog cholera, has reached a similar conclusion.

In a case of an æstivo-autumnal malaria described by Flexner, hyaline necrosis of the hepatic cells exhibited a remarkably con-

[1] Atti del R. accad. med. di Roma, 1887, p. 247.
[2] Johns Hopkins Hospital Reports, 1895, vol. v. p. 379.
[3] Cent. f. allg. Path. und path. Anat., 1896, Bd. vii. p. 321.
[4] Compt. rend. de la Soc. de biol., 1893, p. 469.
[5] Johns Hopkins Hospital Reports, 1897, vol. vi. p. 259.
[6] Journal of Medical Research, 1903, vol. ix. p. 146.

stant relation to the central vein, often completely surrounding it. In a second case, in which the wall of the cæcum and colon contained necrotic, tumor-like nodules, areas of necrosis, having a similar relation to the central veins of the lobules, were found in the liver. Mallory, studying the liver from a large number of autopsies (1190), has noted necrosis about the central veins in 95 instances and has designated the lesion "central necrosis," in order to distinguish it from the more commonly recognized focal necrosis. Central necroses were found chiefly with acute infectious diseases, notably with diphtheria, acute endocarditis, lobar pneumonia, acute peritonitis, and epidemic cerebrospinal meningitis. In 45 cases the lesion was complicated with cardiac disease. Bacteriological examination of various organs was made in 83 cases and in 40 instances streptococcus pyogenes was present; in 15, diplococcus lanceolatus; in 12, bacillus diphtheriæ; and in 10, staphylococcus pyogenes aureus. Mallory thinks that the lesion is due to the presence in the circulation of strong toxins most frequently derived from streptococcus pyogenes. It is probable, he thinks, that the lesion occupies the center of the lobule, because the cells are here somewhat poorly nourished.

In 51 instances Mallory found focal necrosis of the liver. In one case, which is included in this group, the lesions were distributed with much regularity, forming often a definite zone in the outer third of the lobule, but not reaching to the periphery; in some lobules the necroses were irregularly distributed and reached to or surrounded the central vein. Masses of streptococci were found throughout the liver, but chiefly in the necrotic areas, where fibrin was abundant.

In order to obtain information concerning the frequency, the distribution and the etiology of hepatic necrosis occurring in well-defined lobular zones, I have examined the liver from each of 500 autopsies. In 33 instances necrosis of the focal character defined by Flexner and others were present; in 16 of these cases the lesion was associated with typhoid fever. In 39 instances, on the contrary, the foci of necrosis exhibited a definite relation to the lobulation of the organ, usually occupying one or other of the zones already described.

Central Necrosis. In 12 instances necrosis of the hepatic cells was limited to the central zone of the lobule. In this group are included only those cases in which the necrotic areas exhibit

a definite relation to the central vein, wholly or partially surrounding it in many if not in all lobules. While in some cases each central vein is surrounded by a zone of necrotic cells extending approximately half the distance to the portal space, in others the necrosis is less extensive and less regularly disposed, extending outward a distance much less than half the radius of the sectioned lobule. In 4 instances the lesion has been associated with fatty metamorphosis of the hepatic cells throughout the entire central zone. In the liver of a child which died from malarial fever the entire central part of the lobule, extending half the distance from the central vein to the periphery, was the seat of intense fatty degeneration. Only in this area, often encircling the central vein, fat-containing cells have undergone necrosis.

In a considerable proportion of the cases central necrosis of the hepatic lobule has been associated, with evident disturbances of circulation. In half the number capillary vessels in the central part of the lobule have been markedly dilated, while in two-thirds lesions of the heart—endocarditis or pericarditis, or of the blood-vessels, arterial sclerosis—have been present. While such vascular disturbances may predispose to the lesion the essential factor is doubtless in most instances some form of acute infection. In one instance death was the result of malarial fever. Typhoid fever was present in one case, but was associated with fibrinopurulent pericarditis caused by a tuberculous lymph gland which had penetrated the esophagus, thus producing a sinus in contact with the pericardium. Cultures made at autopsy from the pericardial exudate remained sterile. In 5 instances streptococcus pyogenes was isolated from one or more organs at autopsy and in 2 cases there was general infection with micrococcus lanceolatus.

Closely related to the group of central necroses just described are the not infrequent instances in which advanced chronic passive congestion of the liver is associated with coagulative necrosis affecting the periphery of the congested zone. Mallory has noted the association of these two lesions and finds that the necroses adjoin the congested area, forming a ring of necrotic cells or appearing as small necrotic areas in the middle zone. This zone in the cases of chronic passive congestion which I have examined has been found in the periphery of the congested area and has varied much in position and in extent. In the greater number of examples the congested area has extended approximately two-thirds of the dis-

tance from central vein to portal space. The peripheral half of this area of congestion, being necrotic, constitutes a geometrical middle zone, which does not correspond with the previously defined mid-zone of necrosis affecting the uncongested liver. The latter, which doubtless depends upon physiological peculiarities of the hepatic circulation, lies closer to the periphery of the lobule. With chronic congestion dilatation of capillaries is associated with corresponding atrophy of the columns of liver cells; immediately about the central vein atrophy of cells is most marked, but those which are present are often otherwise normal and have well-preserved nuclei. In the necrotic zone forming the periphery of the congested area cells are hyaline and their nuclei are degenerate or wholly absent. Fibrin is often abundant, particularly within the capillaries.

The necrosis of chronic congestion, like the more typically central necroses, are usually referable to terminal infections occurring perhaps in the course of some long-standing disease of the valvular apparatus of the heart. In 9 of 11 cases cultures were obtained at autopsy. In 1 instance both streptococcus pyogenes and staphylococcus pyogenes aureus were obtained from the blood of the heart and from other organs; in 3 additional cases streptococcus pyogenes was obtained from more than one organ, while in 2 cases streptococcus pyogenes and in 1 case staphylococcus pyogenes aureus was obtained at autopsy from a single organ.

Peripheral Necrosis. In only 4 of the 500 cases examined has necrosis been found in the peripheral zone of the hepatic lobule. It is noteworthy, moreover, that peripheral necrosis has occurred only in association with pregnancy, 3 cases being examples of the characteristic hepatic lesion of eclampsia described by Jürgens, Schmorl and others. The liver is studded with hemorrhagic foci varying much in size. In such areas the liver cells have undergone necrosis and have lost their nuclei. The body of the cell, losing its definite outline, is merged with the dense network of fibrin which makes its appearance throughout the necrotic tissue. Abundant hemorrhage has occurred into and about the necrotic tissue. Schmorl has described as anemic necrosis somewhat similar lesions unassociated with hemorrhage. Jürgens, Schmorl and others have noted that the smallest necrotic areas are always in contact with the portal spaces; in the three cases which I have studied this distribution has been well illustrated. Though necrosis frequently occupies a fairly uniform zone surrounding the portal space, it may extend

a variable distance toward the central vein. The tissue of the portal space is often implicated in the necrotic process, and both portal vein and hepatic artery may undergo thrombosis. The lesion is not uniformly present in the periphery of each lobule, and not infrequently the hepatic cells about a portal space are normal.

A fourth case without symptoms of eclampsia has defined with much greater regularity than those just cited a peripheral zone within the lobule, for hyaline necrosis is accurately confined to that peripheral part of the hepatic lobule which in examples of midzonal necrosis has remained normal. Moreover, the lesion presents certain histologic characters which serve to distinguish it from the lesion of eclampsia; there is no marked tendency to hemorrhage, and fibrin is not found within the zone of necrosis, the capillary vessels being unobstructed. Since the lesion is in these respects unique, the important features of the case will be mentioned.

CASE I.—Mrs. B., aged twenty-three years, was admitted in labor to the service of Dr. Williams in the Johns Hopkins Hospital. The present pregnancy had had a normal course. Cæsarean section had been performed four years before on account of a generally contracted pelvis. The same operation was again found necessary. Subsequently symptoms of intestinal obstruction developed and an operation for their relief was undertaken; enterostomy was performed. Death occurred several hours later, six days after admission.

Anatomical Diagnosis. Operation wound; perpetual uterus, suppurative metritis; acute general peritonitis; chronic pulmonary tuberculosis; parenchymatous degeneration of the kidneys.

The liver weighs 1270 grams; the tissue has a bright-yellow color and the lobulation is distinct, the central veins of the lobules being somewhat injected. Microscopic examination shows that a peripheral zone in each lobule is defined with great regularity by necrosis of the hepatic cells. This zone has a width which equals from one-fifth to one-fourth the distance from portal space to central vein. The parenchymatous cells are hyaline and in many instances their nuclei have disappeared. The capillary vessels are well preserved and contain no fibrinous thrombi. Polynuclear leukocytes are numerous in the necrotic zone.

MIDZONAL NECROSIS. In the liver from 500 autopsies necrosis limited to the middle zone previously defined has been noted in 9

cases. Studying additional material the same lesion has been found in five instances. From these examples its character and perhaps its etiology may be determined. The liver affected with the lesion has not been notably enlarged, the weight varying in adults from 1600 to 2000 grams. The substance of the organ has been usually pale, but its color has varied considerably, being largely dependent upon the presence or absence of fatty metamorphosis. An intermediate zone in five instances has been recognizable by the naked eye as a deep-red circle within each lobule. In these five cases the liver on section has had a bright-yellow color, but more careful examination has disclosed a peculiar mottling; the centers of the lobule have a pale-yellow color and are surrounded by a narrow, bright-red, circular band, outside of which peripheries of the lobule are yellow or grayish-yellow.

Microscopic examination has usully shown that all of the parenchymatous cells in the middle zone have become hyaline, losing their usual granular appearance and staining deeply with eosin. Occasionally their protoplasm is broken up into hyaline globules or droplets which take the same homogeneous stain. The affected cells are diminished in size. Occasionally all of the cells in the middle zone are not affected and necrotic cells occur besides those which are little changed. In almost all instances, however, necrosis is complete and the hepatic cells no longer retain their columnary arrangement. The nuclei of the affected cells have disappeared completely or exhibit various stages of degeneration, being shrivelled and stained deeply by the nuclear dye. A conspicuous feature of the lesion rendering it in some instances recognizable to the naked eye is the hemorrhage which occurs into the zone of necrosis. Red blood corpuscles are numerous outside the capillary vessels of which the walls are still intact. Polynuclear leukocytes accumulate in moderate number and occasionally are found to have penetrated into necrotic cells. Fibrin, which is not infrequently found in similar necrotic lesions, has not been observed in the specimens examined.

In two instances necrotic cells in a narrow but well-defined middle zone have been partially or completely removed and regenerative changes have been found in progress. In such a circular zone the columns of hepatic cells are broken, being represented by a few hyaline cells without nuclei or particles of such cells. Cells, however, are numerous and are in large part lymphoid or plasma cells.

The capillary vessels are dilated, and in one instance the zone was recognizable to the naked eye as a red ring within each lobule.

Those conditions which produce necrosis in the middle zone of the hepatic lobule, acting upon the parenchyma elsewhere, are doubtless capable of causing intense fatty degeneration, for the two lesions frequently coexist. In 10 of the 14 cases studied accumulation of fat has been so extensive that it must be regarded as a degenerative change. In most instances fat has been limited to the central zone of the lobule, the hepatic cells in the periphery being normal. In three instances both the central and peripheral zones contained fat in great abundance, so that in a specimen stained with osmic acid the midzone of necrosis has been clearly defined by the absence of fat within it. (See Fig. 2.) There is usually no evidence that the cells which have undergone hyaline necrosis were the seat of fatty degeneration; occasionally, however, hyaline cells are vacuolated as if by fat.

Midzonal-like central necrosis of the hepatic lobule is so frequently associated with intense bacterial infection that the latter must be regarded as the most important etiological factor concerned in its production; chronic congestion, however, has no part in the production of the midzonal lesion.

In 6 of the 14 cases which have been studied the lesion has accompanied acute general peritonitis, usually of fibrinopurulent type. In four cases peritonitis followed intraperitoneal operations, one of which was undertaken for the relief of typhoid perforation; in a fifth case peritonitis followed puerperal infection and was associated with pyæmia, while in the sixth instance it was preceded by gonorrhœal endometritis in a child aged fourteen years. In two cases streptococcus pyogenes alone was isolated from the peritoneal cavity; in one of these cases general infection with this organism followed puerperal endometritis. In a third case both streptococcus pyogenes and bacillus coli were isolated; in the case of peritonitis after typhoid perforation bacillus coli and bacillus lactis aerogenes were isolated from the peritoneal cavity. In one case bacillus proteus vulgaris was the only organism isolated, occurring in the blood from the heart and in other organs; while in one case satisfactory bacteriological examination was not possible.

Lesions of the gastrointestinal tract were the predominant feature in three instances of midzonal necrosis. In one case gastroenterostomy for removal of carcinoma of the pylorus was followed by local-

ized peritonitis and bacillus coli was isolated from various organs. In a second case with extensive ulcerative colitis streptococcus pyogenes and bacillus coli were found in the liver and kidney. In the third case adenocarcinoma of the sigmoid flexure of the colon was accompanied by extensive ulceration and necrosis; no bacteriological examination was made.

Of the remaining 5 cases of midzonal necrosis 2 were instances of general infection with streptococcus pyogenes; in one of these cases puerperal infection was followed by suppurative thrombosis and vegetative endocarditis, and in the other suppuration of the anterior mediastinum followed œsophagotomy for the removal of a foreign body. In a third case pyæmia and suppurative arthritis were present, but satisfactory bacteriological examination was not possible; staphylococcus pyogenes aureus and albus were isolated from an incised abscess of the leg. In one of two remaining cases acute cystitis followed a gunshot wound of the spinal cord, bacillus proteus vulgaris being isolated from the heart's blood and kidney at autopsy; in the other case an aneurysm of the aorta compressed the trachea, causing fibrinous tracheitis and bronchopneumonia; bacillus coli was isolated from the lungs and spleen, but otherwise bacteriological examination was unsatisfactory.

In the group of zonal necrosis must be classified several remarkable instances of necrosis causing complete destruction of parenchymatous cells throughout those parts of the lobule which have been designated central and middle zones, and sparing only a small marginal band which corresponds to the peripheral zone previously defined. In the following case typhoid fever complicated by intestinal obstruction and laparotomy has been associated with almost uniform necrosis of both central and middle zones.

CASE II.—The patient, a woman, aged twenty-two years, was admitted to the service of Dr. Kelly. Double salpingectomy was performed one month before the onset of the fatal illness. A second laparotomy was performed two weeks later for the relief of intestinal obstruction due to adhesions. Seventeen days before death the temperature rose and remained elevated. A third laparotomy was undertaken for the relief of symptoms of intestinal obstruction; death occurred three days later. The urine contained albumin and casts.

Anatomical Diagnosis. Typhoid fever; hyperplasia and necrosis of Peyer's patches; acute splenic tumor; fatty degeneration and

necrosis of the liver; acute nephritis; wound of laparotomy and salpingectomy; localized fibrinous peritonitis.

The liver weighs 1750 grams. The central part of each lobule has a brick-red color and is surrounded by a zone of bright yellow. Microscopic examination demonstrates that the parenchymatous cells in the greater part of each lobule have undergone hyaline necrosis, leaving intact a narrow peripheral zone, in width about one-fifth the radius of the lobule. In this peripheral zone in immediate contact with the necrotic area the hepatic cells are the seat of fatty degeneration. The endothelium of the capillaries which are dilated is well preserved; red blood corpuscles are found in the tissue outside the vessels.

The kidneys, which together weigh 460 grams, are much enlarged. The swollen cortex has a yellowish-red color mottled with small areas of yellow color. The epithelial cells of the tubules have occasionally undergone coagulation necrosis and many hyaline casts are present.

In the two cases to follow necrosis has affected both the central and middle zones, but in the latter the hepatic cells have been the seat of more advanced disintegration. In the central part of the lobule the hepatic cells retain their columnar arrangement, though they are almost uniformly hyaline and without nuclei; occasional parenchymatous cells about the central vein are preserved. In the midzone columnar arrangement of the necrotic cells is lost and they are in large part broken and disintegrated.

CASE III.—A child ten years of age, admitted to the service of Dr. Halsted, had given evidence of gonorrhœal infection followed by abdominal pain and vomiting. Eight days after the onset of these symptoms general peritonitis was discovered at operation. The peritoneal cavity was irrigated with normal salt solution. Death followed two days later.

Anatomical Diagnosis. Acute salpingitis; acute fibrinopurulent peritonitis with beginning organization of the exudate; necrosis and fatty degeneration of the liver; acute nephritis.

The liver weighs 850 grams. The centers of the lobules are red and the peripheral parts are pale yellow. Hyaline necrosis has destroyed each lobule, leaving intact a narrow peripheral margin of which the width is about one-fifth the radius of the lobule. The columnar arrangement of the hepatic cells is well preserved except

in a zone occupying the periphery of the necrotic areas, and hence corresponding to the midzone already described. Here the cells are often broken into particles and are no longer in contact with one another. The peripheral zone in which the cells are still preserved is the seat of fatty metamorphosis, which is most advanced next the necrotic tissue.

The cortex of the kidneys, which together weigh 250 grams, is considerably swollen. Microscopic examination shows that the cells of the convoluted tubules are swollen and granular and have in places undergone coagulative necrosis; tubules contain hyaline casts.

Bacteriological examination demonstrated the presence of micrococcus gonorrhœæ in the peritoneal exudate. Streptococcus pyogenes was isolated from the blood in the heart, from the uterus, the urinary bladder and the lung. Bacillus coli was found in the heart's blood and in the peritoneal cavity.

Through the kindness of Dr. J. Whitridge Williams I am permitted to add the following case which occurred in his practice. The autopsy was performed by Dr. H. T. Marshall.

CASE IV.—The patient, a primipara, aged twenty-eight years, was first seen by Dr. Williams during the second month of pregnancy. At this time she complained of nausea and vomiting, which became so persistent that rectal feeding was necessary. Vomiting nevertheless continued, and she grew rapidly weaker and more emaciated. The vomitus contained blood in small amount. On the twenty-fifth day after the patient was first seen it was decided to bring on an abortion and the uterus was emptied without difficulty. For eighteen hours nausea and vomiting ceased, but returned with much severity. Weakness became extreme, torpor was followed by coma, and death occurred three days later. The temperature remained normal until the day of death, when it rose to 101.6° F. Jaundice was not present before death.

Anatomical Diagnosis. Puerperal uterus; laceration of cervix uteri and of vagina; necrosis and fatty degeneration of the liver; jaundice; acute nephritis; chronic pulmonary tuberculosis.

The liver is of small size, weighing 1000 grams. The tissue is soft and on section has a bright-yellow color. Microscopic examination shows that the central part of each lobule has undergone necrosis, leaving intact only a narrow peripheral zone. Immediately about

the central vein of the lobule nuclei of the endothelial cells and rarely nuclei of hepatic cells are preserved, but elsewhere both have wholly disappeared. In the peripheral part of the necrotic areas, occupying a zone in width about one-fifth the radius of the lobule, parenchymatous cells are broken into particles and have lost their columnar arrangement. In the central part of the lobule necrotic cells are vacuolated as if the seat of fatty degeneration. In the peripheral zone nucleated hepatic cells in contact with the necrotic tissue have undergone advanced fatty degeneration.

The kidneys, which are bile-stained, are of large size; the cortex, which measures from 7 to 8 mm. in width, is yellow and opaque. No bacteriological examination was made.

Mallory has found that coagulative necrosis may almost completely destroy each hepatic lobule, leaving intact only a narrow zone in contact with the portal spaces, and has pictured the liver from such a case. Stone[1] has recently described and pictured a case which closely resembles that of Dr. Williams just described. Necrosis of the liver, leaving in each lobule a narrow peripheral margin of well-preserved cells, followed persistent vomiting during the second and third months of pregnancy. Though jaundice was absent the case is regarded as an example of acute yellow atrophy of the liver. Stone adds the statement that toxemia in pregnancy may be accompanied by hepatic necrosis affecting cells in a zone intermediate between the central vein and the periphery of the lobule, but makes no further comment upon this lesion.

The Relation of Midzonal Necrosis to Acute Yellow Atrophy of the Liver. The three cases just described are closely related on the one hand to the preceding examples of midzonal necrosis. On the other hand they present a close similarity to the condition somewhat inaccurately known as acute yellow atrophy of the liver. Indeed, when the cases of midzonal necrosis are grouped with the three instances of combined central and midzonal necrosis, the etiology and pathology of these lesions present many analogies to those of the far rarer acute yellow atrophy.

Atrophy of the liver is not an essential feature of the disease which under the name icterus gravis is characterized by rapidly increasing jaundice, delirium and other cerebral symptoms, vomit-

[1] American Gynecology, 1903, vol. iii. p. 518.

ing, and often fever. In the early stage of this disease, according to Liebermeister,[1] Orth[2] and other writers, the liver is enlarged rather than diminished in size. Among 94 cases of icterus gravis collected by Liebermeister, in 57 the liver was atrophied; in 47 of these cases the duration of the disease was more than nine days. Of 37 cases in which the liver was enlarged or little diminished in size in only 10 had the disease lasted more than nine days. At this early stage the liver has not yet assumed the mottled yellow and red appearance which is due to the presence of hemorrhagic areas in which disintegration of the hepatic substance is far advanced; the tissue has an almost uniform bright-yellow or ochre-yellow color. Such has been the appearance of the liver when midzonal necrosis has been associated with fatty degeneration; the cut surface has a bright-yellow color and the lobulation of the organ is marked only by the hemorrhagic character of the necrotic zones.

The nature of the degenerative change affecting the hepatic parenchyma in cases of acute yellow atrophy has not been accurately defined. Some writers describe a simple necrosis of the hepatic cells, attributing the fat which is present to accessory conditions; others think that the parenchymatous cells undergo a severe form of fatty degeneration ending in destruction. Meder[3] emphasizes the necrotic character of the change and suggests that those cells which are least injured exhibit fatty degeneration. A similar explanation is applicable to the frequent association of midzonal necrosis and advanced fatty degeneration. The middle zone being subjected to the most intense action of the injurious agent undergoes necrosis, while the central zone becomes the seat of fatty change or less frequently of necrosis. In some instances the peripheral zone as well undergoes fatty degeneration, but is rarely necrotic.

Destruction of parenchyma in cases of acute yellow atrophy may affect the entire lobule, but frequently hepatic cells about the central vein survive. According to Meder the central part of the lobule is preserved when the liver has a uniform yellow or yellowish-brown color and the same condition is present in the yellow parts of the mottled livers. Marchand[4] has described regenerative changes both in the centre and in the periphery of the lobule. In the latter situation the tubular structures which resemble newly formed bile-

[1] Deutsche med. Woch., 1892, Bd. xviii. p. 1090.
[2] Lehrbuch der speciellen pathologischen Anatomie, Berlin, 1893.
[3] Ziegler's Beiträge, 1895, Bd. xvii. p. 143. [4] Ibid., p. 206.

ducts are derived, he believes, from pre-existing interlobular bile-ducts. The possibility that they represent in part altered columns of hepatic cells cannot be excluded with certainty.

With zonal necrosis, as with acute yellow atrophy, degenerative changes in the liver are usually accompanied by analogous changes in the kidneys. During life the urine has contained albumin and casts. The epithelial cells of the cortical tubules have been found the seat of fatty degeneration and have occasionally undergone coagulative necrosis.

Midzonal necrosis, like acute yellow atrophy, has occurred more frequently in females than in males. Of 17 instances, including three examples of combined midzonal and central necrosis, 10 occurred in females and 7 in males. The correspondence between these figures and those of Legg[1] (of 100 cases of acute yellow atrophy 69 in females), and those of Thierfelder[2] (of 143 cases, 88 in females) is perhaps in part accidental. The relationship of acute yellow atrophy to pregnancy has long been recognized. In Legg's statistics 25 of 69 cases in women were associated with pregnancy; in Thierfelder's statistics 33 of 88 cases in women followed pregnancy. Three of ten instances of midzonal necrosis in women have accompanied pregnancy.

Acute yellow atrophy of the liver occurs in individuals previously in good health, but may be secondary to a variety of infectious diseases. The etiological factors concerned are doubtless not always the same. Meder has collected eighteen cases in which the disease has been observed in association with secondary syphilis. Cases of acute yellow atrophy following a variety of diseases due to bacterial infection are described. Sabourin[3] has described acute yellow atrophy accompanying typhoid fever. Dörfler[4] has recorded an instance of the disease occurring during the course of typhoid fever complicated by cholelithiasis. Particularly noteworthy is a case described by Cahn,[5] in a girl seventeen years of age, acute yellow atrophy of the liver accompanied diphtheria affecting the tonsils and extending to the mucous membrane of the stomach. Bacterial inflammation of the stomach has been associated with acute yellow atrophy of the liver in a case described by Van Heukelom,[6] who has

[1] On the Bile, Jaundice, and Bilious Diseases, New York, 1880.
[2] von Ziemssen's Cyclopædia, 1880 (Trans.), vol. ix. p. 238.
[3] Revue de méd., 1882, p. 600.
[4] Münchener med. Woch., 1889, p. 878.
[5] Deutsches Arch. f. klin. Med., 1884, Bd. xxxiv. p. 118.
[6] Quoted by Meder.

emphasized the probability that the hepatic lesion is caused by toxic material absorbed from the domain of the portal circulation. Instances are recorded in which acute yellow atrophy of the liver has followed puerperal infection, erysipelas, osteomyelitis, and other diseases usually caused by pyogenic micrococci. Especial attention has been directed to the relation between streptococcus pyogenes and acute necrosis of the liver by Babes,[1] who has recorded five cases illustrating this association. He cites a similar case described by Nepveu and Bourdillon.[2]

The etiological factors concerned in the production of midzonal necrosis present much similarity to the foregoing, the lesion being frequently associated with pyogenic infections, especially those caused by streptococcus pyogenes. Midzonal necrosis has occurred three times in pregnant women, and in two instances has been associated with puerperal infection. In two instances the lesion has followed typhoid fever, but in both cases the disease has been complicated by conditions requiring operative interference.

It appears probable that necrosis of the middle zone of the hepatic lobule, or of the combined middle and central zones, is an early stage of the process which has its termination in acute yellow atrophy. The former lesion, however, is so frequently the result of grave infection, notably of acute general peritonitis, that death follows before secondary changes in the altered liver are possible. The liver is enlarged rather than atrophied and the characteristic symptoms of acute yellow atrophy have not been present during life. In one instance of zonal necrosis jaundice was observed at autopsy, but had so recently appeared that it was not recognizable before death.

[1] Virchow's Arch., 1894, Bd. cxxxvi. p. 1.
[2] Gazette méd. de Paris, 1892, No. 12.

THE RELATION OF CELLS WITH EOSINOPHILE GRANULATION TO BACTERIAL INFECTION.[1]

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In a preceding article I have described the behavior of the eosinophile cells during the course of experimental infection with a parasite belonging to the animal kingdom, namely, Trichina spiralis. Both the polynuclear leukocytes with fine granulation and the coarsely granular eosinophile leukocytes of the blood are increased in number, but increase of eosinophile cells constitutes the predominant feature of the local and hæmal leukocytosis which results. Infection with a large variety of bacteria, on the contrary, causes migration of finely granular leukocytes into tissues where bacteria or their products have accumulated, and, in addition, hæmal leukocytosis occurs. The behavior of the leukocytes with eosinophile granulation in the presence of bacterial infection, though repeatedly the subject of investigation, has not been clearly defined.

That the eosinophile cells have a part in resisting bacteria which have entered the body was first suggested by Hankin,[2] who maintained that the bactericidal substances of the blood serum are derived from leukocytes with eosinophile granulation. Answering a critical review of this theory by Metschnikoff,[3] Hankin[4] subsequently stated that his observations made upon rabbits had reference to the amphophile or pseudoeosinophile cells of Ehrlich, and not to the coarsely granular cells which correspond to the eosinophile leukocytes of human blood.

[1] The present investigation has been conducted with the aid of a grant from the Rockefeller Institute for Medical Research.

[2] Cent. f. Bakt., 1892, vol. xii. pp. 777, 809

[3] Ann. de l'Inst. Pasteur, 1893, vol. vii. p. 50.

[4] Cent. f. Bakt., 1893, vol. xiv. p. 852.

Kanthack and Hardy,[1] following the suggestion of Hankin's hypothesis, studied in the frog the behavior of the eosinophile leukocytes in the presence of micro-organisms. If bacillus anthracis were injected below the skin of a frog, eosinophile cells, they found, accumulated in large numbers during the first three or four hours and collected in masses about the bacilli. Large cells with non-granular protoplasm and large nuclei, called by Kanthack and Hardy hyaline cells, then made their appearance, entered the masses of eosinophile cells, and finally ingested the bacteria. The micro-organism became the prey of the hyaline cell only after it had been subjected to the influence of eosinophile cells. Such influence, according to Kanthack and Hardy, is exerted by the granules of these cells. In hanging drops they saw the granules stream toward that side of the cell which happened to be in contact with the micro-organism and then gradually disappear.

Hardy and Wesbrook[2] have shown that when fresh cultures of the bacillus of anthrax or of the spirillum of cholera are injected into the intestine of frogs, eosinophile cells migrate through the epithelium into the lumen, so that they finally disappear from the intestinal wall.

Mesnil,[3] studying the means by which lower vertebrates resist bacterial infection, has repeated many of the experiments of Kanthack and Hardy, but has not obtained the same results. Within two and a half hours after injection of bacillus anthracis into the dorsal lymph sac of the frog non-granular leukocytes with round or lobed nuclei begin to accumulate and immediately approach and ingest the bacteria. Leukocytes with eosinophile granulation may congregate at the point of inoculation, but their number is inconstant, and, while in some instances they constitute from 50 per cent. to 80 per cent. of the leukocytes at the site of inoculation, they are often, particularly in Rana esculenta, not 1 per cent. of those present. That cells with eosinophile granulation in lower vertebrates do not play an essential part in resisting bacterial invasion is, Mesnil believes, further shown by the fact that the perch (Perca fluviatilis), which is not susceptible to bacillus anthracis, possesses no granular leukocytes; injected anthrax bacilli, as in the frog, are engulfed

[1] Philosophical Transactions of the Royal Society of London, 1894, vol. clxxxv., B., part i. p. 279; and Proceedings of the Royal Society, 1894, vol. lii. p. 267.

[2] Journal of Physiology, 1895, vol. xviii. p. 490.

[3] Ann. de l'Inst. Pasteur, 1895, vol. ix. p. 801.

by non-granular leukocytes possessing irregularly round or lobed nuclei. In accordance with the view held by Metschnikoff and himself, Mesnil believes that the eosinophile granules represent transformed material previously ingested by the leukocyte; such old phagocytes filled with reserve material still possess some remains of their phagocytic power. Mensil states that he has observed these cells in the frog ingest bacteria, rarely after subcutaneous inoculation, but more frequently after the injection of bacteria into the circulation.

In a previous paper[1] I have reviewed the evidence which demonstrates, I believe, that the eosinophile cells of mammals are not derived from the polynuclear leukocytes with finer granulation, but exclusively from eosinophile cells in the bone-marrow. These cells of the marrow, which may be designated eosinophile myelocytes, are analogous to the myelocytes with finer granulation, the parent cells of the finely granular leukocytes. In lower vertebrates the relation of the various granular leukocytes to one another and to those of higher mammals is less clearly understood. In birds, for example, the more common polynuclear leukocytes are provided with large spindle-shaped granules, which, like the less numerous coarsely granular leukocytes of mammals, have a strong affinity for eosin. Hence, conclusions reached by a study of lower vertebrates, some of which apparently possess no granular leukocytes, even were they in accord, are not with our present knowledge applicable to mammals.

In the article just mentioned I have considered certain facts which indicate that the polynuclear leukocytes with fine and with coarse granules in different mammalian species bear corresponding relations to one another. A second series of experiments performed by Kanthack and Hardy[2] on rabbits, guinea-pigs, and rats has, therefore, a more direct bearing upon the activities of the eosinophile cells in man and in other higher mammals. In mammals, as in lower vertebrates, according to Kanthack and Hardy, those wandering cells which are first attracted by micro-organisms and a variety of other irritant substances are coarsely granular oxyphile (eosinophile) cells, which have their origin in the neighboring connective tissue. This conclusion has been based upon a series of experiments

[1] American Journal of the Medical Sciences, 1904, vol. cxxvii. p. 217.
[2] Journal of Physiology, 1894, vol. xvii. p. 81.

in which various bacteria and a variety of substances, such as nitrate of silver, turpentine and filtrates from bacterial cultures have been introduced into the peritoneal cavity or into the subcutaneous tissue of the animals just named.

If Ziegler's chambers containing cultures of bacillus anthracis or of the spirillum of cholera are introduced into the peritoneal cavity of the rabbit, at the end of seven hours only coarsely granular eosinophile cells have succeeded in entering. When a less virulent organism, such as bacillus ramosus, is employed, large non-granular cells with round or indented nuclei ("hyaline cells") have accumulated in large numbers at the end of two and a half hours. The more virulent bacteria, according to Kanthack and Hardy, cause rapid destruction of these non-granular cells, while the less virulent organism allows them to accumulate. In another series of experiments Kanthack and Hardy have injected bacillus anthracis, bacillus pyocyaneus or the spirillum of cholera in small amount into the peritoneal cavity of the guinea-pig or of the rat. The primary result has been disappearance of the cells present in the cavity, and as fragments of eosinophile cells are to be found in the peritoneal fluid, they are believed to have been destroyed in part at least. The injected bacteria are quickly attacked by the coarsely granular cells, and even within five minutes after the inoculation of bacillus anthracis into the rat 40 per cent. of the eosinophile cells found are applied to bacilli. These cells do not ingest bacteria, but their granules, Kanthack and Hardy have maintained, exhibit the phenomenon noted in the frog. Bacteria are engulfed by the "hyaline" cells, the process beginning within ten minutes after inoculation. Destruction and removal of bacteria, they conclude, is due to the combined activity of two kinds of cells, the coarsely granular oxyphile (eosinophile) and the "hyaline" cell.

Durham[1] has studied the local reaction which occurs when various bacteria are injected into the peritoneal cavity of guinea-pigs. He has failed to observe the preliminary attack of eosinophile cells described by Kanthack and Hardy, and reaches the conclusion that these cells have no important part in the destruction of bacteria. Durham says, however, that in animals which die within thirty hours after inoculation, the only cells in the peritoneal fluid at the time of death are finely granular polynuclear leukocytes in abun-

[1] Journal of Pathology and Bacteriology, 1897, vol. iv. p. 388.

dance, together with a variable number of coarsely granular leukocytes. At times only one coarsely granular cell is seen in ten fields of the $\frac{1}{12}$ objective, while in other instances one may be found in almost every field. Judged by their relative numbers, the eosinophile cells at this stage, Durham believes, can have but a small share in the work of destroying bacteria.

Noesske[1] has performed experiments with the tubercle bacillus which have a bearing upon the present subject. Studying this organism under conditions which cause it to assume a radiate formation suggesting actinomycosis bovis, he found at an early stage of infection, about such colonies of the bacillus, free granules, which, he thought, were derived from eosinophile cells. He supported his views by demonstrating that the granules react to stains like eosinophile granules and are similarly affected by digestive ferments, but does not bring more conclusive evidence of their nature. Introduction of tubercle bacilli into the muscle of rabbits showed more clearly that eosinophile cells accumulate at the seat of infection. Colonies of bacillus tuberculosis were placed within an incision made into the muscle of the back, and at the end of four days the surrounding tissue was removed. In immediate contact with the implanted colonies the tissue was necrotic; polynuclear leukocytes were numerous, and eosinophile cells were few. Nearby, however, eosinophile leukocytes were present in great number within degenerate muscle fibres, among which were scattered tubercle bacilli. A similar result was produced in rabbits with tubercle bacilli killed with steam. Noesske, moreover, obtained an accumulation of eosinophile cells in the subcutaneous tissue of a human subject by injecting the dead bacilli. He reaches the conclusion that these cells are always abundant during the first stage of tuberculous infection. Pyogenic bacteria, on the contrary, Noesske found caused no accumulation of eosinophile cells.

Ehrlich[2] found that with acute leukocytosis only the mononuclear and neutrophile polynuclear forms of the blood are increased, while the eosinophile cells exhibit an apparent diminution. Subsequent observers have noted a well-marked diminution of the eosinophile leukocytes during various infectious diseases caused by bacteria. Müller and Rieder[3] have found that eosinophile cells are diminished

[1] Deutsche Zeitsch. f. Chirurgie, 1900, vol. lv. p. 211.
[2] Zeit. f. klin. Med., vol. i. part iii.
[3] Deutsches Arch. f. klin. Med., 1891, vol. xlviii. p. 47.

during typhoid fever. Rieder[1] observed their diminution or complete absence from the blood in cases of pneumonia, while Canon[2] noted a diminution in association with septic processes. Zappert[3] has carefully studied the behavior of the eosinophile leukocytes during the course of various infectious diseases, and reaches the conclusion that fever is associated with such constant diminution of the absolute number of these cells that this diminution may be regarded as one of the manifestations of febrile intoxication. With pneumonia, typhoid fever, erysipelas and certain pyogenic infections eosinophile cells are diminished so long as fever persists, but after its subsidence they return to normal or, in a certain proportion of cases, undergo a more or less well-marked increase above their normal number. Zappert quotes observations of Ehrlich[4] upon the destruction of leukocytes in the spleen during febrile processes, and reaches the conclusion that eosinophile cells are diminished because the normal transformation of leukocytes with neutrophile granulation into eosinophile leukocytes is prevented.

Observations similar to those of Zappert have been made by Türk[5] and others in cases of pneumonia, typhoid fever, diphtheria and with various suppurative processes. It is, however, noteworthy that in certain diseases not due to bacterial infection, such as scarlet fever (Kotschetkoff[6]) and smallpox (Ferguson[7]), there is a moderate increase of eosinophile cells.

In hardened tissues which have been the seat of a variety of inflammatory processes several observers have noted the presence of eosinophile cells, occasionally in considerable number. Numerous observations have shown that eosinophile cells are often abundant in carcinomata of the cervix uteri, in nasal polyps, and in a variety of other benign and malignant tumors. From a study of tissues obtained at autopsy and from the operating table, Noesske[8] reached the conclusion that tumors of mucous membranes, particularly when they are exposed to injury, are rich in eosinophile cells; immense numbers are not infrequently found in epitheliomata of the lip or

[1] Beiträge zur Kenntniss der Leukocytoses, Leipzig, 1892.
[2] Deutsche med. Woch., 1892, vol. xviii. p. 206.
[3] Zeit. f. klin. Med., 1893, vol. xxiii. p. 227.
[4] Zur Kenntniss des acuten Milztumors, Charité-Ann., 9 Jahr.
[5] Klinische Untersuchungen über das Verhalten des Blutes bei Infectionskrankheiten, Wien und Leipzig, 1898.
[6] Ref., Cent. f. allg. Path. u. path. Anat., 1892, No. 11.
[7] Journal of Pathology and Bacteriology, 1903, vol. viii. p. 411.
[8] Loc. cit.

of the tongue, in carcinomata of the cervix uteri, and in laryngeal tumors. Tumors situated below the skin contain eosinophile cells when the overlying epithelium is lost and ulceration is beginning. When benign or malignant tumors are situated in internal organs where they are protected from infection, eosinophile cells are scant or absent. Noesske thinks that these cells have a part in protecting the tissue from bacterial infection. Where, however, the tumor tissue is the seat of an advanced inflammation, and, indeed, in the lesions of various pyogenic or other inflammatory processes, such as erysipelas, osteomyelitis and pneumonia, eosinophile cells are present in small number or are completely absent. Eosinophile cells, at times in very large number, have been found by Howard and Perkins[1] in the lesion of appendicitis, salpingitis, oöphoritis and perioöphoritis, acute interstitial and suppurative nephritis, enteritis and of a variety of other inflammatory processes. Their association with such lesions has not been found constant, and in some instances they are normally present in the affected tissue.

In an article to which reference has already been made, I have collected evidence to show that the bone-marrow is the seat of origin of the eosinophile leukocytes, and the vascular system the path by which they are distributed to various tissues of the body. Changes in the blood being subject to observation during the entire course of an experimental infection, it is possible to determine if the eosinophile cells of the blood exhibit a characteristic reaction to bacterial invasion.

Methods. In counting the relative and absolute number of eosinophile leukocytes in the blood, I have used the methods previously described.[2] For the purpose of these experiments the guinea-pig has been found particularly suitable, since the blood of apparently healthy full-grown animals usually contains from 5 per cent. to 10 per cent. of eosinophile leukocytes. Hence the effect of conditions which cause a diminution of these cells can be far more accurately determined than in animals possessing only a very small proportion of such cells. In order to test the behavior of the eosinophile cells, I have employed a variety of bacteria, including bacillus tuberculosis, bacillus anthracis, bacillus choleræ suis and bacillus mucosus capsulatus (of Friedländer), all of which are pathogenic in small quantity for guinea-pigs. Bacillus pyocyaneus has been selected as a convenient means of studying the effect of a relatively severe

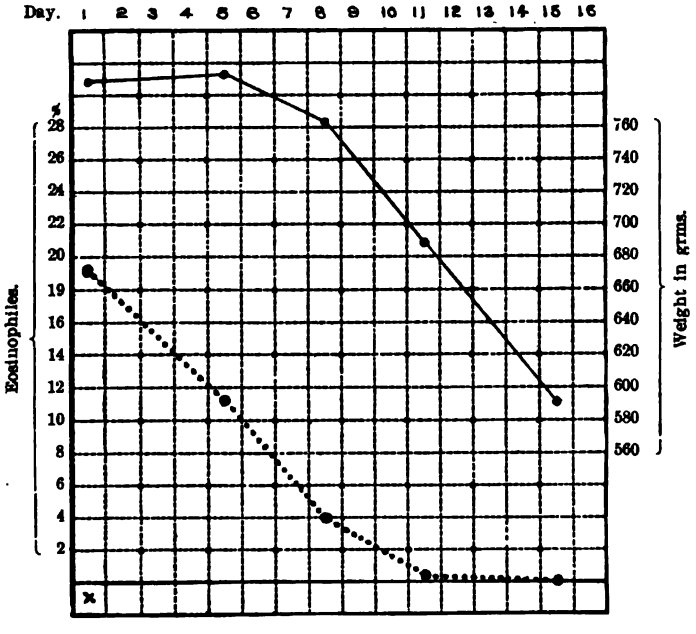
[1] Johns Hopkins Hospital Reports, 1902, vol. x. p. 249. [2] Loc. cit.

infection from which the animal is capable of recovering. Bouillon cultures incubated from twenty-four to forty-eight hours have been employed in varying amount. The injection of as much as 3 c.c. of sterile bouillon into the peritoneal cavity has caused no noteworthy change in the number of eosinophile cells nor in the weight of the animal.

Behavior of the Eosinophile Leukocytes during the Course of Fatal Bacterial Infection.

Infection of guinea-pigs with a moderate number of trichina, I have shown,[1] causes a gradual increase of the eosinophile leuko-

CHART I.



Showing changes in the percentage of eosinophile leukocytes (dotted line) and in weight (straight black line), caused by infection with bacillus tuberculosis. The day of inoculation in this and in subsequent charts is marked by a ×.

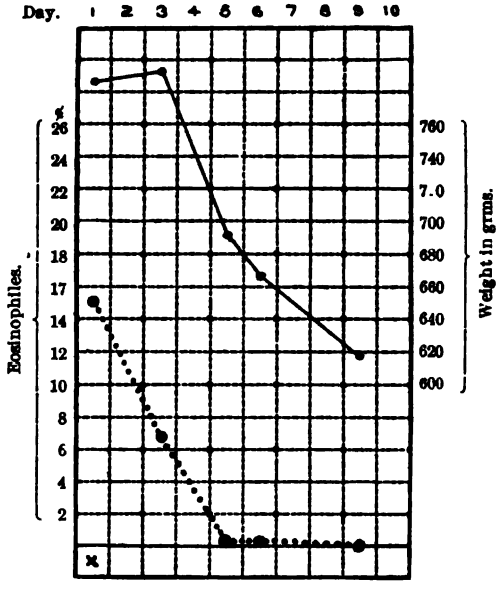
cytes, but death is preceded by rapid diminution. The administration of a very large number of parasites is more quickly fatal; the

[1] American Journal of the Medical Sciences, 1904, vol. cxxvii. p. 477.

eosinophile cells diminish in number and completely disappear from the blood. The effect of fatal bacterial infection is similar, though the eosinophile cells may disappear from the circulating blood more gradually.

Chart I. records the proportion of eosinophile leukocytes in the blood and the weight of a large guinea-pig which received into the subcutaneous tissue of the abdominal wall 0.5 c.c. of a suspension in bouillon of bacillus tuberculosis. Four days before death eosinophile cells had almost completely disappeared from the blood.

CHART II.



Showing changes in the percentage of eosinophile leukocytes (dotted line) and in weight (straight line), caused by infection with bacillus choleræ suis.

Chart II. records the percentage of eosinophile cells and the weight of a large animal which received subcutaneously 0.5 c.c. of a bouillon culture of bacillus choleræ suis incubated twenty-four hours. Death did not occur until the ninth day, but the eosinophile leukocytes, which at the beginning of the experiment constituted 15 per cent. of the white blood corpuscles, had almost completely disappeared on the fifth day.

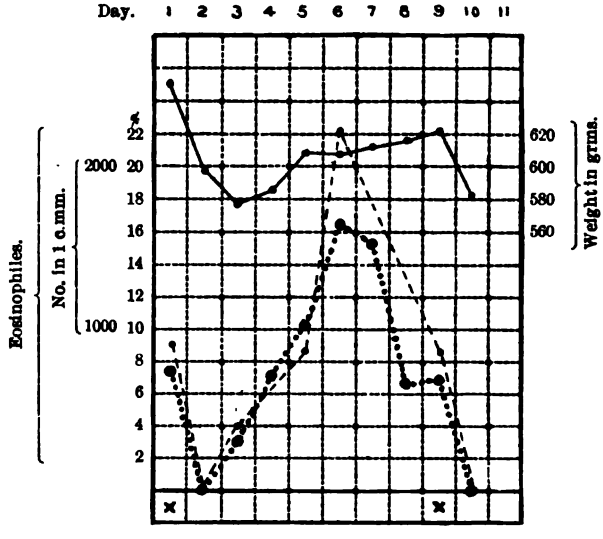
In both experiments the tissues from the animals were hardened in Zenker's fluid and stained, after embedding in paraffin, with hematoxylin and eosin, so that eosinophile cells might be identified. The paucity of eosinophile cells in the tissues in both experiments is in harmony with their disappearance from the blood. In the spleen, where the number of eosinophile cells normally present corresponds approximately to their number in the circulating blood, no eosinophile cells are found. In the mucosa of the small intestine, even in the neighborhood of Peyer's patches, none have been found in the sections examined. In a mesenteric lymphatic gland from the animal injected with the bacillus of hog cholera only a few scattered eosinophile cells are found. Particularly remarkable is the small number of cells with eosinophile granulation present in the bone-marrow; myelocytes occur, but are sparsely scattered, while the almost complete absence of smaller eosinophile cells with lobed nuclei is noteworthy. In the bone-marrow from both animals occur very small eosinophile cells, with a diameter approximately two-thirds that of an eosinophile leukocyte. These dwarfed cells have nuclei which are round or only slightly indented, resembling in the latter case intermediate stages between the nucleus of the myelocyte and the typically lobed nucleus of the mature eosinophile leukocyte.

With bacterial infections which are more acute than those just described, eosinophile leukocytes disappear much more quickly from the circulating blood; indeed, none may be found in specimens examined at the end of a few hours. Injection of 1 c.c. of a bouillon culture of bacillus pyocyaneus, incubated four days, into the peritoneal cavity of a guinea-pig possessing 5.7 per cent. of eosinophile leukocytes, caused their disappearance within twenty-four hours; death occurred at the end of forty hours. Subcutaneous inoculation of 0.5 c.c. of a twenty-four-hour culture of the same organism caused the percentage of eosinophile leukocytes to fall from 9.7 to 0.5 in eight hours. Bacillus mucosus capsulatus (0.3 c.c. of a bouillon culture forty eight hours old injected into the peritoneal cavity) caused the eosinophile leukocytes to diminish during four hours from 20.7 per cent. to 7.3 per cent. of the number of white blood corpuscles. The injection of streptococcus pyogenes into the peritoneal cavity had a similar effect; 1 c.c. of a culture four days old caused the eosinophile leukocytes of a guinea-pig possessing 5.7 per cent. to diminish to such an extent that none were found in a specimen examined at the end of four hours.

Behavior of Eosinophile Leukocytes during the Course of Non-fatal Bacterial Infection.

The disappearance of eosinophile leukocytes under the influence of severe, usually fatal infections has suggested the desirability of studying their behavior during the course of acute infections from which the animal is capable of recovery. For this purpose bacillus pyocyaneus has been selected and has been injected into the peri-

CHART III.

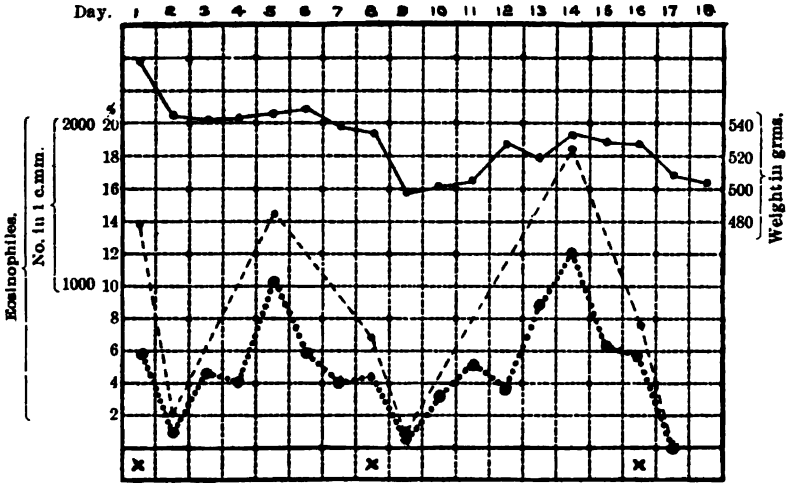


Showing changes in the percentage (dotted line) and in the absolute number (broken line) of eosinophile leukocytes after infection with bacillus pyocyaneus. On the first day 0.7 c.c. of a bouillon culture twenty-four hours old was injected, and on the ninth day this dose was repeated. The animal was killed on the tenth day. The weight is indicated by an unbroken straight line.

toneal cavity in order to avoid the prolonged effect of a localized abscess. The injection of 0.5 c.c. to 1 c.c. of a culture in bouillon incubated at 37° C. during twenty-four hours causes an acute general peritonitis, from which the animal usually recovers. The well-known effect of such inoculation upon the blood being an increase of the polynuclear leukocytes with fine granulation, I have limited my attention to the behavior of the eosinophile cells.

Chart III. records the effect of the intraperitoneal inoculation of 0.7 c.c. of a bouillon culture of bacillus pyocyaneus upon a large guinea-pig of which the eosinophile leukocytes constituted 7.3 per cent. of the white corpuscles. At the end of twenty-four hours after inoculation eosinophile leukocytes had diminished to such extent that none were found in the specimens of blood examined. The proportion gradually rose and reached a maximum on the sixth day, when it exceeded that originally present; on the eighth day the percentage count agreed approximately with that before inoculation. The absolute number of eosinophile cells has been estimated from the total number of leukocytes, counted daily by the same Thoma-Zeiss apparatus, and the changes which it undergoes are found to correspond with those of the percentage count. The weight of the animal has been recorded, since it gives an indication of the effect of infection upon the general metabolism of the animal.

CHART IV.



Showing the effect of infection with bacillus pyocyaneus. On the first day 0.5 c.c., on the eighth day 1 c.c. of a culture twenty-four hours old was injected; on the sixteenth day the animal received 1 c.c. of a culture four days old, and death occurred on the eighteenth day.

Chart IV. is appended in order to confirm the results just described. The small dose (0.5 c.c.) of bacillus pyocyaneus injected on the first day was followed by a much less marked increase of eosino-

philes than that consequent upon the second larger dose (1 c.c.). In these experiments, as in that recorded by Chart III., decrease of eosinophile cells to almost complete disappearance is the first effect of inoculation; a somewhat gradual increase follows and reaches a maximum on the fifth or sixth day, when, after inoculating 0.7 c.c. or 1 c.c. of the culture, the number of eosinophile cells in 1 c.mm. of blood is more than twice the original number. A return to normal then follows. Such changes in the blood suggest that destruction of eosinophile cells has been followed by regeneration causing an accumulation in excess of the normal. In order to obtain an explanation of this phenomenon it is essential to know the cause of their temporary disappearance during what may be termed the stage of eosinophile leukopænia.

In order to determine the fate of the eosinophile leukocytes which have disappeared from the peripheral circulation during the early stages of acute bacterial infection attention has been directed to the seat of infection. For the study of the local changes which follow inoculation the peritoneal cavity offers obvious advantages. The inflammatory exudates which accumulate can be readily obtained while the phenomena occurring in the tissues can be conveniently studied in preparations made from the transparent tissue of the omentum and mesentery.

Local Accumulation of Eosinophile Leukocytes after Intraperitoneal Inoculation of Bacteria.

Since previous studies have shown that local accumulation of eosinophile cells is the result of their migration from the blood-vessels, it has been considered desirable to study with especial care the contents of the vessels at the site of inoculation and to note perhaps the occurrence of migration. For this purpose the following method has been employed: At the end of a variable time after inoculation the animal is etherized and, while breathing still continues, the peritoneal cavity is opened in the midline. After specimens of the peritoneal exudate have been prepared, Zenker's fluid (containing 5 per cent. of acetic acid) warmed to a temperature of 40° C. is poured into the cavity. The omentum and mesentery, together with the peritoneum elsewhere, are thus quickly hardened. The tissues to be preserved are removed and kept in Zenker's fluid about twenty-four hours, after which they are treated in the usual

way. Small pieces of the omentum and mesentery are stained without embedding. Treatment of these membranes, previously stained with hæmatoxylin, with 0.5 per cent. aqueous solution of eosin has served to demonstrate so clearly the granules of the eosinophile leukocytes that these cells are readily distinguishable from the more numerous polymorphonuclear leukocytes with fine granulation; at the same time they are recognizable within the blood-vessels. The amœboid shape of the leukocytes is often well preserved and not infrequently they are fixed in process of migration from the vessels. Methylene blue used with eosin has the advantage of staining bacteria.

The peritoneal cavity contains normally a small amount of clear fluid in which are suspended a considerable number of cells. The character of these wandering cells has been the subject of special study by Kanthack and Hardy, who found the following varieties: 1. Polymorphonuclear cells with coarse eosinophile granules forming in guinea-pigs from 30 per cent. to 50 per cent. of the total number of cells. 2. Cells with basophile granulation occurring in small number. 3. Small cells, identical with the lymphocytes of the blood, possessing a single round nucleus surrounded by a narrow rim of protoplasm. 4. Larger mononuclear cells with round or indented nuclei and fairly abundant non-granular protoplasm. The latter Kanthack and Hardy designate "hyaline cells." Both Durham and Beattie have found in the peritoneal cavity of guinea-pigs three types of wandering cells described by Kanthack and Hardy, but have not noted the presence of cells with basophile granulation. The "hyaline cells" of these authors in part at least are the macrophages of Metschnikoff.

Before describing my observations upon the behavior of eosinophile cells in the presence of bacterial infection I will briefly define the reaction which occurs when bacteria are injected into the peritoneal cavity. These changes have been studied by Issaeff,[1] Metschnikoff,[2] Durham,[3] and Beattie.[4] The first effect of intraperitoneal inoculation is the partial disappearance of cellular elements normally present, so that in the guinea-pig, according to Durham, five or six minutes after injection almost all cells save lymphocytes have disappeared.

[1] Zeit. f. Hygiene, 1894, vol. xvi. p. 287.
[2] Ann. de l'Inst. Pasteur, 1895, vol. ix. p. 369.
[3] Journal of Pathology and Bacteriology, 1896, vol. iv. p. 338.
[4] Ibid., 1903, vol. viii. p. 129.

This stage of leukopænia persists about one hour (Durham), during which time the amount of peritoneal fluid increases. Metschnikoff has maintained that the disappearance of leukocytes is the result of their destruction by the toxic products introduced with the micro-organisms. Durham has brought forward evidence to support a different explanation. At the end of only two minutes after injection he has noted that "hyaline" and eosinophile cells begin to adhere in clumps, the lymphocytes being exempt. At first these groups are small, but later large masses containing many cells may be found. Such masses tend to adhere to the peritoneal surfaces, but especially to the omentum, so that at the end of about twenty minutes (Durham) "hyaline" and eosinophile cells are here present in considerable number. At the end of about an hour polynuclear leukocytes with fine granulation make their appearance, and subsequently accumulate so that about fifteen hours after inoculation they are present in enormous number. They are actively phagocytic and ingest bacteria. If, however, infection is caused by a large dose of a virulent organism, few polynuclear leukocytes may be found, and the stage of leukopænia may persist until death. With a relatively mild infection which has caused the accumulation of polynuclear cells in great number, cells of another type appear at the end of about fifteen hours. They are larger than polynuclear leukocytes and have large round, oval or indented nuclei. These cells, which are the macrophages of Metschnikoff, are actively phagocytic and ingest not only bacteria but polynuclear leukocytes as well, so that frequently several of the latter are seen within one macrophage. Upon the fourth, fifth or sixth day after infection, the peritoneal fluid has assumed its normal characters, disappearance of the polynuclear leukocytes being followed by that of the macrophages.

Observers who have studied the foregoing phenomena have not failed to note the presence of eosinophile cells in the exudate which accumulates. Such cells, however, exist in the normal peritoneal cavity, and the difficulty of determining whether they are increased or diminished is considerable. The divergent conclusions reached by observers who have studied the effect of intraperitoneal inoculation have already been cited.

Study of the blood has shown that eosinophile cells partially or completely disappear from the peripheral circulation within a few hours after intraperitoneal inoculation. Study of the membranes

which are contained within the peritoneal cavity has explained this phenomenon. Eosinophile cells constitute a considerable proportion of the immense number of leukocytes which within several hours are attracted to the bloodvessels which abut upon the infected peritoneal surface. Their migration and accumulation within the peritoneal cavity are demonstrable. These facts may be best illustrated by a series of experiments performed with *bacillus pyocyaneus*. The following observations have been made upon fourteen animals inoculated intraperitoneally and killed after intervals varying from a few minutes to twenty-four hours:

Within a few minutes after the injection of one cubic centimeter of a bouillon culture of bacillus pyocyaneus incubated twenty-four hours large mononuclear and eosinophile cells disappear from the peritoneal cavity, so that in animals killed at the end of eight and fifteen minutes after inoculation only one or two eosinophile leukocytes have been encountered while counting several hundred cells, almost exclusively lymphocytes. Examination of the omentum fixed and stained confirms the statements of Durham. Large mononuclear cells form compact clumps, often containing a hundred or more cells, among which are eosinophile cells in varying number. Altered or fragmented eosinophile cells were not seen, and evidence that these cells had undergone destruction was not obtained. In animals killed at the end of eight, fifteen, or thirty minutes after inoculation the number of leukocytes within the bloodvessels of the omentum and mesentery has undergone no change. Within small veins, having a diameter equal or twice that of a polynuclear leukocyte, white corpuscles are scattered among the red corpuscles at such long intervals that the labor of counting them is considerable. In the tissue of the mesentery eosinophile cells occur in considerable number, but are not more numerous than in the normal animal.

At the end of one hour the number of cells in the peritoneal exudate is still small, though polynuclear leukocytes with fine granulation have made their appearance. Eosinophile cells are also present in small number. In the tissue of the mesentery a few polynuclear leukocytes are found about many of the bloodvessels. Within the lumen of the vessels leukocytes are much more numerous than before, and are in large part finely granular polynuclear leukocytes, some of which are flattened out upon the endothelial surface of the vessel, while others are in process of migration.

At the end of two hours the same changes are more advanced. In the peritoneal exudate cells are not numerous, and about one-half of those present are polynuclear forms with fine granulation; eosinophile cells are fairly numerous and constitute about 10 per cent. Leukocytes have accumulated within the bloodvessels of the mesentery and are often found in fair number about them, while cells in process of migration are numerous. Eosinophile cells are present both in the tissue and within the bloodvessels, but their proportion does not differ notably from that in the peripheral circulation before inoculation. In an animal (weight 553 grams) in which the eosinophile leukocytes numbered 5.7 per cent. before inoculation, 4 per cent. were counted in small veins in diameter about twice that of a polynuclear leukocyte. Since, however, the total number of leukocytes within these vessels has been enormously increased, such percentage indicates that many eosinophile cells have been held in the vessels of the inflamed region. Eosinophile cells are occasionally found in process of migration.

At the end of four hours the influence of bacterial infection upon the eosinophile leukocytes is more clearly demonstrable. The omentum is now covered by purulent exudate and, as Durham has described it, is rolled into a compact mass lying in contact with the stomach. In the peritoneal cavity is a considerable amount of turbid fluid containing an immense number of cells which are almost wholly polynuclear leukocytes. Eosinophile cells are present, but in small number, so that one or two are encountered while counting successive hundreds of cells. In the tissue of the mesentery polynuclear leukocytes are numerous and eosinophile cells are present in smaller proportion. In the bloodvessels leukocytes are closely crowded and eosinophile cells are very numerous. In blood from the ear of a guinea-pig weighing 604 grams the eosinophile leukocytes which had constituted 8.3 per cent. of the white corpuscles before inoculation had fallen at the end of four hours to 1.3 per cent. The animal was killed within the next half-hour. In small veins of the mesentery with a diameter from three to four times that of a polynuclear leukocyte, 21, 26, 20 and 23 eosinophile leukocytes were counted in successive hundreds of white corpuscles, which were here present in very large numbers. In smaller vessels with a diameter approximately half as great, leukocytes were less numerous and a smaller number of eosinophile cells were present, the count in two successive hundreds being 11 and 13. Where eosinophile cells are so numerous

the process of migration is readily demonstrable. Some cells with eosinophile granulation are flattened and closely applied to the inner surface of the vessel; others have been fixed while making their way through the wall of the vessel, part of the cell being still within the lumen, while a part has penetrated the intima and projects upon the outer surface of the small vein which is formed by little more than a layer of endothelial cells. That part of the leukocyte which projects from the vessel wall is occasionally connected with the remainder, still in the lumen of the vessel, by a strand of protoplasm drawn out into a narrow thread. Upon the surface of the omentum polynuclear leukocytes are present in great number and are usually collected to form compact clumps. Within and about such masses eosinophile leukocytes are numerous In the bloodvessels of the omentum, polynuclear leukocytes, both with fine and with coarse granulation, are abundant.

At the end of eight hours polynuclear leukocytes are present in the peritoneal exudate in immense number and are in large part collected into masses held together by a network of fibrin. From 1 to 2 per cent. of eosinophile cells can be counted in the fresh exudate. The masses of leukocytes just mentioned are particularly numerous upon the surface of the retracted omentum. In specimens of the omentum stained with eosin and methylene blue eosinophile cells are clearly demonstrable, even though embedded in masses of finely granular leukocytes, and are particularly numerous within the clumps of leukocytes already mentioned. From such specimens one obtains convincing evidence that eosinophile cells in number far greater than that originally present have found their way into the peritoneal cavity.

Eosinophile leukocytes upon the surface of the omentum are in part normal in appearance and are provided with lobed nuclei which stain most deeply at the periphery. Eosinophile cells exhibiting degenerative changes are, however, readily found. Though the eosinophile granules are still well preserved, the nucleus of the cell is contracted into one or more small round masses which stain deeply and homogeneously. While the finely granular leukocytes almost uniformly contain many ingested bacteria, the bodies of the eosinophile cells are free from such inclusion.

Examination of the mesentery demonstrates that leukocytes are less numerous in the small bloodvessels than at an earlier period. Though polynuclear leukocytes and eosinophile cells are still abun-

dant, migration is less active and at the end of sixteen hours has apparently ceased completely.

At the end of sixteen hours eosinophile leukocytes still form a conspicuous feature of the exudate upon the surface of the omentum and to less extent upon the surface of the mesentery. Many are still well preserved, but a considerable proportion exhibit degenerative changes, the nucleus being contracted into one or more small masses of chromatin which stain deeply and homogeneously. Occasionally a clear vacuole is situated within the otherwise compact globule of chromatin. In some instances, on the contrary, the lobed nucleus of the eosinophile cell is swollen and stains poorly. Changes of a similar nature affect the nuclei of the finely granular polynuclear leukocytes. At this stage large mononuclear cells have made their appearance.

At the end of twenty-four hours large mononuclear cells have become numerous. Eosinophile leukocytes form a small proportion of the great number of cells present in the exudate. Ingestion of polynuclear cells by the large mononuclear phagocytes has begun. In this process the eosinophile and finely granular leukocytes are equally concerned, and within a macrophage may be found a round clump of coarse eosinophile granules from which the nucleus has completely disappeared.

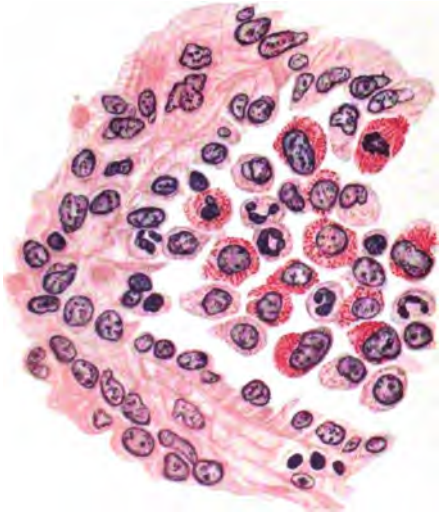
In order to confirm the preceding observations, repeating the experiments, I have employed, instead of bacillus pyocyaneus, bacillus mucosus capsulatus (of Friedländer), an organism far more pathogenic for guinea-pigs.

Experiment A (*Bacillus Mucosus Capsulatus*). An animal weighing 492 grams received 0.3 c.c. of a bouillon culture twenty-four hours old. The eosinophile leukocytes before inoculation constituted 3.3 per cent. of the white blood corpuscles. In the peritoneal exudate at the end of three hours free bacteria are present in large number; polynuclear leukocytes, lymphocytes and eosinophile cells are present, the latter forming 35.3 per cent. In the tissue of the mesentery leukocytes occur in moderate number. In the small veins leukocytes are very numerous, and in four successive hundreds of white corpuscles the proportion of eosinophile leukocytes has been 14, 17, 13 and 17 per cent. Eosinophile cells are found fixed in process of migration.

Experiment B (*Bacillus Mucosus Capsulatus*). An animal weighing 625 grams received intraperitoneally 0.3 c.c. of a culture

FIG. 1.

FIG. 2.



of bacillus mucosus capsulatus forty-eight hours old. The eosinophile leukocytes in the peripheral circulation which before inoculation numbered 24.3 per cent. fell at the end of four hours to 7.3 per cent. The animal was killed at the end of four and a half hours. Cells are fairly numerous in the peritoneal exudate and are almost wholly polymorphonuclear leukocytes and eosinophile cells, the latter constituting 7.7 per cent. In the mesentery (see Plate, Fig.1) polynuclear leukocytes and eosinophile cells occur in considerable number, particularly in the neighborhood of the bloodvessels. In the vessels leukocytes are often accumulated in such number that the lumen is closely packed with cells of which eosinophile leukocytes constitute considerably more than half. To obtain an approximate estimation of their relative number they were counted in small vessels with a diameter from one and a half to twice that of an eosinophile cell; the percentage count was 65 per cent. Many of these cells are found flattened and closely applied to the endothelial surface of the vessel, while others are found in process of migration; a small process containing part of the nucleus may project between the endothelial cells, the remainder of the leukocyte being within the lumen.

Sections of the mesentery embedded in paraffin have confirmed the observations just described. In the lumen of one comparatively small vein differential count showed the presence of 73 per cent. of eosinophile leukocytes.

Experiment C (*Bacillus Mucosus Capsulatus*). A guinea-pig weighing 597 grams, with eosinophile leukocytes numbering 20.3 per cent. received intraperitoneally 0.5 c.c. of a bouillon culture of bacillus mucosus capsulatus. The animal died at the end of twenty hours, and the peritoneal cavity was found to contain about 3 c.c. of turbid fluid in which polynuclear leukocytes numbered 69 per cent., eosinophile cells 29 per cent., and large mononuclear cells 2 per cent.

EXPLANATION OF PLATE.

FIG. 1.—The mesentery of a guinea-pig four hours after inoculation with bacillus mucosus capsulatus stained with hæmatoxylin and eosin, showing migration of eosinophile leukocytes. Leukocytes with eosinophile granulation are readily distinguishable from finely granular polynuclear forms.

FIG. 2.—The spleen of a guinea-pig four hours after inoculation with bacillus pyocyaneus, showing venous sinus containing myelocytes with eosinophile granulation. An eosinophile myelocyte undergoing karyokinetic division is present.

The phenomena which occur after inoculation with bacillus pyocyaneus are reproduced by infection with bacillus mucosus capsulatus. The experiments with the two organisms are not wholly comparable, since the number of eosinophile leukocytes in the circulating blood before inoculation in different animals has differed considerably. Nevertheless, with the more virulent bacillus mucosus capsulatus migration of eosinophile cells appears to be much more active, so that at the end of a given time the proportion of eosinophile leukocytes in the peritoneal exudate is much greater than with bacillus pyocyaneus. The chemotactic influence which virulent bacteria exert upon the eosinophile cells is further shown by study of the bloodvessels in the mesentery. In two of the experiments just described eosinophile leukocytes constituted respectively 65 per cent. and 15.2 per cent. of the total number of white corpuscles in these vessels, through their proportion in the peripheral circulation before inoculation had been only 24.3 per cent. and 3.3 per cent. Doubtless the earlier migration of polynuclear leukocytes with fine granulation explains in part the large proportion of eosinophile leukocytes present in the vessels three or four hours after inoculation. The experiments demonstrate that both types of polymorphonuclear leukocyte are attracted to the inflamed region.

Results of a similar nature have been obtained with *bacillus anthracis*.

Experiment A (*Bacillus Anthracis*). A guinea-pig weighing 533 grams, with eosinophile leukocytes numbering 27.3 per cent., received into the peritoneal cavity 0.5 c.c. of a bouillon culture of bacillus anthracis forty-eight hours old. At the end of four hours the animal was killed. The peritoneal exudate is found to contain polynuclear leukocytes in great number, together with eosinophiles, constituting 7 per cent. of the cells present. In the tissue of the mesentery eosinophile cells are numerous. The small bloodvessels are closely packed with leukocytes, among which those with eosinophile granulation, counted in small veins with a diameter approximately one and one-half that of a leukocyte, constitute in three successive hundreds 23, 21 and 20 per cent.

In the foregoing experiment it is evident that a large number of eosinophile leukocytes have been held in the inflamed area, even though it be recalled that their proportion in the peripheral circulation before inoculation slightly exceeded that found in the vessels

of the mesentery four hours later, for they then constituted one-fifth of the immense number of leukocytes which are crowded together in the vessels of the inflamed membrane. With bacillus anthracis as with bacillus pyocyaneus (see Chart IV.), a small dose of the micro-organism has a less marked influence upon the eosinophile cells.

Experiment B (*Bacillus Anthracis*). A guinea-pig weighing 560 grams, with eosinophile leukocytes in the peripheral circulation numbering 2.3 per cent., was inoculated with 0.1 c.c. of a twenty-four-hour-old culture of bacillus anthracis. At the end of four hours the peritoneal exudate contained polynuclear leukocytes in great number, together with eosinophiles, constituting 2.2 per cent. of the cells present. Of the leukocytes which are closely packed together in the bloodvessels of the mesentery 1 per cent. are cells with eosinophile granulation.

Accumulation of Eosinophile Myelocytes in the Spleen.

Study of the spleen during the first few hours which follow bacterial inoculation of the peritoneal cavity has afforded further evidence of a profound disturbance of the eosinophile cells. In the venous sinuses of the spleen four hours after inoculation are found both finely granular and coarsely granular or eosinophile myelocytes, together with a small number of giant cells identical in structure with the so-called megakaryocytes of the bone-marrow.

When a rabbit is repeatedly bled the spleen undergoes what has been designated by Dominici[1] "myeloid transformation." Cells which are characteristic of the bone-marrow make their appearance in the organ. During the course of prolonged infection with the bacillus of typhoid fever, Dominici has observed a similar phenomenon, but all the cells peculiar to the marrow are not represented, megakaryocytes and eosinophile cells being rare or absent. In the spleen of three guinea-pigs killed eighteen weeks after inoculation with bacillus tuberculosis, Dominici[2] found myelocytes both with fine and with coarse (eosinophile) granulation and megakaryocytes. Dominici believes that new-formation of myeloid tissue occurs in the spleen, so that the organ again takes on the hæmato-

[1] Arch. de médecine expérimentale, 1901, vol. xiii. p. 1.
[2] Compt. rend. Soc. de biol., 1900, p. 851.

poietic activity which it normally possesses only during embryonic life.

Muir, moreover, has found myelocytes in the spleen of rabbits subjected to repeated infection with staphylococcus pyogenes aureus. He has not attempted to distinguish forms with fine and coarse granulation. He has observed similar cells in the circulating blood and thinks that it is a function of the spleen to remove such abnormal elements from the blood.

In the spleen of individuals dead with scarlet fever, diphtheria, erysipelas, septicæmia, pneumonia, peritonitis, purulent meningitis and phthisis Hirschfeld[1] has found both neutrophile and eosinophile myelocytes. Since, he says, myelocytes have been found (Engel,[2] Türk[3]) in the blood in association with the hyperleukocytosis of infectious diseases, it may be suspected that those in the spleen are derived from the bone-marrow. Against this view is the occurrence in the spleen of eosinophile myelocytes which have never been observed in the blood with hyperleukocytosis. Hirschfeld maintains that he has found transitions between the non-granular lymphoid elements of the spleen and the granular myelocytes, which can thus, he thinks, be formed within the organ.

I have observed the occurrence of eosinophile myelocytes in the spleen after inoculation with bacillus pyocyaneus, bacillus anthracis, and bacillus mucosus capsulatus. For control, the spleens from six apparently healthy guinea-pigs have been carefully studied. Eosinophile leukocytes in the circulating blood of these animals just before death varied in different animals from 0.3 to 17.2 per cent. Eosinophile cells which are identical with those of the blood are readily recognizable, both in the sinuses of the spleen and in the intervening pulp, and are particularly numerous when the proportion of eosinophile leukocytes in the blood has been large. Eosinophile myelocytes have not been found. The spleens from two animals which had been killed respectively during the third and fourth week after infection with Trichina spiralis were also examined. In one instance the proportion of eosinophile leukocytes in the peripheral circulation had increased from 5.7 to 17.3 per cent., in the other from 6.7 to 17.7 per cent., the latter figures being noted just before death. Eosinophile leukocytes were present in large

[1] Berliner klin. Woch., 1902, vol. xxxix. p. 701.
[2] Deutsche med. Woch., 1897, Nos. 8 and 9.
[3] Loc. cit.

number in the spleen, both in the sinuses and in the pulp, but eosinophile myelocytes were entirely absent. Megakaryocytes not improbably occur occasionally in the spleen of apparently healthy rodents, but none were found in the spleens of the eight guinea-pigs examined for control.

The accumulation of eosinophile myelocytes in association with other elements which are characteristic of the bone-marrow has been studied in the previously mentioned series of animals killed at varying intervals after inoculation with bacillus pyocyaneus. At the end of one-half and of one hour after inoculation no myelocytes are found. In the spleen of an animal killed at the end of two hours after inoculation an occasional myelocyte with eosinophile granulation is present in the venous sinuses. Two cells with a diameter from three to four times that of a polynuclear leukocyte are identified by their lobed or budding nuclei as megakaryocytes.

At the end of four hours the sinuses of the spleen exhibit a characteristic appearance. (See Plate, Fig. 2.) Within the lumen of the larger sinuses are often found ten or more cells with a diameter almost twice that of an eosinophile leukocyte; the coarse granules which stain deeply with eosin and with acid fuchsin (of the Biondi-Heidenhain mixture) are identical with those of the eosinophile leukocytes, but the nucleus of the cell is large, round or oval, and of vesicular type; one or more well-defined nucleoli are present. Similar cells undergoing karyokinetic division are found, with little difficulty. The chromatin stains deeply and homogeneously, and exhibits the variations characteristic of different stages of indirect division, ranging from the so-called skein formation to the diaster stage. Myelocytes with fine granulation appear to be less numerous than eosinophile myelocytes, but are present in considerable number, and at times have been fixed while undergoing indirect division. Megakaryocytes are found in the sinuses and are usually somewhat larger than those seen at an earlier stage. Polynuclear leukocytes occur in very great number, while eosinophile leukocytes with polymorphous nuclei are sparsely scattered in the tissue.

At the end of eight hours eosinophile myelocytes are present, but are much less numerous than in the spleen just described. Eosinophile leukocytes are rarely found. Megakaryocytes are present. After sixteen hours eosinophile cells have almost completely disappeared from the spleen; after twenty-four hours a small number are

still present, but only one or two may be fond in a single section. At this time megakaryocytes are found in considerable number.

Four hours after inoculation, at a time when eosinophile leukocytes are migrating into the peritoneal cavity and eosinophile myelocytes are numerous in the spleen, the latter may be found occasionally in the bloodvessels elsewhere. In hardened sections eosinophile myelocytes are numerous in the splenic vein, and in several instances have been fixed while undergoing karyokinetic division. In a small vein of the mesentery was found one typical myelocyte.

In order to confirm the preceding observations I have studied the spleen from animals killed after infection with bacillus mucosus capsulatus and bacillus anthracis. Four hours after the injection of 0.3 c.c. of a bouillon culture of bacillus mucosus capsulatus typical eosinophile myelocytes have been found in the spleen, several not infrequently occurring in the sectioned lumen of a large sinus. Small polynuclear eosinophile leukocytes are also present in moderate number. Myelocytes with fine granulation in two instances have been found undergoing karyokinetic division, and one megakaryocyte of relatively small size has been seen.

Four hours after intraperitoneal inoculation with 0.5 c.c. of a bouillon culture of bacillus anthracis fine and coarsely granular myelocytes have been abundant in the venous sinuses of the spleen. One eosinophile myelocyte undergoing karyokinetic division has been found. Megakaryocytes are particularly numerous and vary much in size.

The occurrence of myelocytes together with megakaryocytes in the spleen a few hours after bacterial inoculation, and at a time when leukocytes both with fine and with coarse granulation are attracted in immense number to the seat of inflammation, demonstrates, I believe, that these cells have their origin in the bone-marrow and are temporarily held in the spleen. They occur in smaller number in the circulating blood. It appears probable that bacterial poisons which, Werigo and Jegunow[1] have shown, exert within from twenty minutes to an hour after inoculation a chemotactic influence upon the finely granular leukocytes of the bone-marrow, are in less degree effective in attracting from the marrow cells which are usually fixed within its substance. Myelocytes with both fine and coarse eosinophile granulation, finding their way to the spleen,

[1] Pflüger's Arch. f. Phys., 1901, vol. lxxxiv. p. 451.

are still capable of karyokinetic division, so that in the spleen and in the portal circulation multiplication of polynuclear leukocytes occurs temporarily. Eosinophile cells, both myelocytes and forms with polymorphous nuclei, have within about sixteen hours almost completely disappeared from the spleen, but megakaryocytes are still present.

Conclusions. Certain bacteria (bacillus tuberculosis, bacillus choleræ suis) producing somewhat chronic, fatal infection in guinea-pigs cause the eosinophile leukocytes to gradually disappear from the circulating blood. After death few eosinophile cells can be found in those tissues in which they are usually present in abundance. Hence the study of tissues removed at autopsy gives little indication of the behavior of the eosinophile leukocytes during the course of bacterial infections. During more acute infections produced by inoculating bacteria into the peritoneal cavity (bacillus mucosus capsulatus of Friedländer, streptococcus pyogenes) eosinophile leukocytes rapidly disappear almost completely from the peripheral circulation within a few hours.

After the inoculation of an organism (bacillus pyocyaneus), producing an infection from which the animal is capable of recovering, eosinophile leukocytes disappear from the peripheral circulation, so that their proportion may fall from 5 to 10 per cent. to less than 1 per cent. The number of eosinophile leukocytes then increases, and at the end of four or five days both the relative and absolute number of these cells may considerably exceed that present in the peripheral circulation before inoculation. At the end of six or seven days the number of eosinophile leukocytes is again normal.

When bacteria (bacillus pyocyaneus, bacillus mucosus capsulatus, bacillus anthracis) are introduced into the peritoneal cavity of the guinea-pig the large mononuclear and eosinophile cells contained in the peritoneal fluid form compact clumps which adhere in great part to the surface of the omentum, so that for a time eosinophile cells have almost completely disappeared from this fluid. At the end of about an hour they have again made their appearance. Some of the eosinophile cells normally present in the tissues of the mesentery and omentum doubtless make their way into the cavity, but soon eosinophile cells begin to accumulate in the bloodvessels of both membranes, but particularly in those of the mesentery. These cells adhere to the wall of the small veins and migrate into the surrounding tissue. This process begins about one hour after inocula-

tion, reaches its maximum several hours later, and is more marked the larger the quantity of bacteria introduced and the more virulent the organism employed. At the end of about four hours, when the number of eosinophile leukocytes in the peripheral circulation has undergone well-marked diminution, the same cells have accumulated in great number in the vessels of the inflamed mesentery and omentum. Similar changes are less marked below the peritoneum of the abdominal wall and below the serosa of the viscera. Though eosinophile cells are migrating from the bloodvessels into the peritoneal cavity, their relative number in the peritoneal exudate diminishes, and at the end of four hours is only 1 or 2 per cent. Polynuclear leukocytes at this time have accumulated in such immense number that they constitute an overwhelming proportion of the cells present.

Eosinophile cells are present in the cavity at the time of inoculation, but only after a period of about an hour do they begin to accumulate in increasing numbers. A primary attack of eosinophile cells such as that described by Kanthack and Hardy has not been observed. Polynuclear leukocytes with fine granulation accumulate in great quantity upon the surface of the omentum and form compact clumps held together by a network of fibrin; eosinophile leukocytes in large number penetrate into these masses of cells. Unlike the polynuclear leukocytes eosinophile cells rarely if ever, acting as phagocytes, ingest bacteria.

Eosinophile leukocytes upon the surface of the omentum, doubtless under the influence of the bacterial poisons, undergo degenerative changes of which nuclear fragmentation is the most characteristic. In such cells the eosinophile granules are still preserved. Evidence that the cells discharge these granules has not been obtained. At a somewhat later period eosinophile leukocytes are ingested by large mononuclear cells (macrophages).

Under the influence of severe bacterial infection eosinophile myelocytes together with other elements, usually regarded as characteristic of the bone-marrow, accumulate in the spleen and may be found in the circulating blood. The occurrence of this phenomenon within from two to four hours after inoculation demonstrates that these elements are derived from the bone-marrow and are not formed in the spleen. Myelocytes both with fine and with coarse (eosinophile) granulation, which have found their way to the spleen, here multiply by karyokinetic division.

Bacteria exert a chemotactic influence upon cells with eosinophile granulation, attracting them from the circulating blood to the site of inoculation and from the bone-marrow into the blood. Eosinophile leukocytes, like the finely granular polynuclear leukocytes, accumulate in the neighborhood of bacteria injected into the body, and, though they rarely act as phagocytes, have a part in the series of changes which follow bacterial invasion.

DISCUSSION.

DR. MELTZER. Dr. Opie stated to-day that in bacterial diseases there is a diminution of eosinophiles in the peripheral circulation. In a previous paper he made the statement that trichinæ cause an increase in the eosinophiles. May we deduce that there is a certain contrast between bacterial diseases and diseases due to some animal organisms with regard to the production of eosinophilia? We may perhaps thus explain the slight increase of eosinophiles in smallpox and scarlet fever, which, according to the latest investigations of the Harvard Pathological Studies, are apparently of protozoic origin.

DR. OPIE: There is certainly a contrast between the action of an animal parasite such as Trichina spiralis and the effect of bacteria. With trichinosis leukocytosis is due in part to an increase of the eosinophile cells and in part to an increase of the ordinary polynuclear leukocytes, but multiplication of eosinophile cells constitutes the predominant feature of the process. There is a certain similarity in the action of bacteria. The first effect of bacterial infection is a diminution of the eosinophile cells, but, as I have shown, this diminution, due to migration of the eosinophile leukocytes, is followed by an increase of these cells in the blood should the animal survive the infection. Hence, increase of eosinophile cells may occur with bacterial infections, but increase of the more common polynuclear forms is predominant. Both the toxins formed by the animal parasites and bacterial poisons are chemotactic for the two forms of cells; with the animal parasite there is an increase of both forms, the eosinophiles predominating, while with bacterial infection both are increased, but the finely granular polynuclear type predominates.

Scarlet fever and smallpox have been cited as infectious diseases not caused by bacteria and accompanied by increase of eosinophile leukocytes in the blood. I am not familiar with any observations upon the blood during the course of yellow fever. During the course of malarial fever there is a slight increase of the eosinophile leukocytes between the paroxysms, but a slight diminution during the paroxysm.

ANALYSIS OF FORTY-TWO CASES OF VENOUS THROMBOSIS OCCURRING IN THE COURSE OF TYPHOID FEVER.

By W. S. THAYER, M.D.,
OF BALTIMORE.

In connection with some studies in which we have recently been engaged concerning the cardiac and vascular complications and sequels of those cases of typhoid fever which have been observed in the last fourteen and a half years in Dr. Osler's wards at the Johns Hopkins Hospital, I have gathered together a few statistics with regard to the cases of venous thrombosis which are, it seems to me, of a certain interest.

Out of 1463 cases of typhoid fever there have been 39 instances of venous thrombosis, a percentage of 2.6+.

In addition to these, two similar cases were admitted during convalescence, while one man who had suffered from double iliac thrombosis coming on during typhoid fever, entered the hospital for treatment two years later.

Mortality. In 5 of the 39 cases occurring in the hospital there was a fatal result—12.3 per cent. In 2 instances the thrombosis was the direct cause of death, once (No. 27855) through pulmonary embolism from a thrombus of the left axillary vein, and once (No. 28600) from the dislodging of a piece of a thrombus in the left iliac vein, with resulting embolism of the inferior cava and right auricle.

Distribution of the Lesions. (*a*) *As to Section of the Body.* The seat of the thrombus was:

In the lower extremities	in 40 instances.
In the upper extremity	" 1 instance.
In the pulmonary artery	" 1 "

Abdominal arteries in a case of double iliac thrombosis of typhoid origin.

(*b*) *As to the Side of Body.* The occluded vessel was:

On the left side	in 26 cases.
On the right side	" 5 "
On both sides	" 9 "
Imperfect records	" 2 "

(*c*) *As to the Vessel Affected.* The affected vessels were:

The femoral vein	in 21 instances.
The popliteal vein	" 5 "
The iliac vein	" 5 "
The veins of the calf alone	" 5 "
The internal saphenous	" 3 "
The pulmonary artery alone	" 1 instance.
The pulmonary artery and common iliac	" 1 "
The axillary vein	" 1 "

TIME OF ONSET OF THE SYMPTOMS. In 39 cases developing in the hospital the time of onset was as follows:

	Weeks.												
1	2	3	4	5	6	7	8	9	10	11	12	13	?
1	1	10	9	5	3	2	4	0	1	1	0	1	1

SYMPTOMS. 1. *Fever.* In 36 of our 39 cases the development of the thrombosis was associated with fever. In 3 there was no fever. In 26 cases the fever was intercurrent, the thrombosis coming on before complete defervescence. In 13 the temperature was normal at the time of onset.

2. *Chills.* In 11, or 28.2 per cent., of these 39 cases the complication was associated with chills. In 2 instances the chills occurred just at the time of recognition of the thrombosis. In 2 cases the chills occurred before recognition; once four days and once a week before. In 6 cases the chills occurred during the complication, once during the period of subsidence, and in the other 5 instances during the height of the process. Once the chills occurred before, during and after the onset of the thrombosis. In one of the 3 cases entering the hospital after the acute symptoms had passed a history of chills during the course of the fever was obtained, though their relation in time to the development of the thrombosis was not clear.

3. *Pain.* The first definite symptom of the thrombosis in every instance was pain. This varied considerably in intensity and suddenness of onset.

In all the cases of *femoral thrombosis* but one there was pain along the course of the femoral vein. In this one instance the only symptoms noted in the hospital were those of popliteal thrombosis. The subsequent history of the case, however, made it clear that there must also have been plugging of the femoral vein.

The first localizing symptom of the process was:

Pain along the course of the femoral vessels and in Scarpa's triangle	in 9 cases.
Pain in the calf	" 5 "
Pain in the popliteal region	" 1 case.
Unsatisfactory note	" 3 cases.
Patient to ill to localize pain	" 1 case.

In 3 of these cases the onset of the pain was strikingly sudden.

In the 5 cases of *popliteal thrombosis* the first localizing symptom in every instance was pain in the popliteal region.

In the 5 cases of *iliac thrombosis* the onset was associated with sudden sharp abdominal pain in 4 instances. In 1 of these cases the pain was extremely severe and associated with leukocytosis. Perforation was suspected, and exploratory laparotomy was performed.

In the 5 cases of *thrombosis of deep veins of the calf* the first symptom in every instance was pain in the calf.

In the 3 cases of *thrombosis of the internal saphenous vein* alone, the first symptom in every instance was pain along the course of the vein.

4. *Œdema.* In all of the 39 cases there was swelling of the affected part. In most instances the temperature was raised, and in a number of cases there was redness over the affected vessel. A definite note as to the existence of œdema was unfortunately not made in all instances.

(*a*) In 19 cases of femoral thrombosis:

Œdema was noted	in 11 cases.
"Swelling" alone	" 6 "
No œdema	" 2 "

(*b*) In 5 cases of iliac thrombosis there was:

Œdema	in 2 instances.
No œdema	" 3 "

(*c*) In 5 cases of popliteal thrombosis there was :

Œdema	in	2 instances.
"Swelling"	"	1 instance.
No note	"	1 "
No œdema	"	1 "

(*d*) In 5 instances in which the deep veins of the calf were apparently alone involved there was :

Œdema	in	1 case.
"Swelling"	"	3 cases.
No œdema	"	1 case.

(*e*) In all 3 cases in which the internal saphenous and veins of the calf were involved there was œdema.

5. *Palpability of the Thrombotic Mass.* In 16 out of the 39 cases the thrombotic mass was felt as a palpable cord.

6. *Leukocytosis.* In 22 cases counts of the colorless corpuscles were made during the complication.

The leukocytes were over 20,000	in	8 cases.
" " " 15,000 to 20,000	"	8 "
" " " 10,000 to 15,000	"	6 "
" " " 9,000 to 10,000	"	8 "
" " " 8,000 to 9,000	"	1 case.
" " " 7,000 to 8,000	"	1 "
" " " 6,000 to 7,000	"	2 cases.
" " " 2,000 to 3,000	"	1 case.

It will thus be seen that in 12, or 54.5 per cent., the leukocyte count was above 10,000, while in 15, or 66.1 per cent., it was over 9000. The highest count, 24,864, occurred in a case of iliac thrombosis in the third week of typhoid fever. In this instance an exploratory laparotomy was performed in view of the possible existence of perforative peritonitis. The lowest count, 2700, occurred on the day after the onset of a thrombosis, apparently of the popliteal, which occurred in the sixth week without fever and with very slight general symptoms.

In eight instances only was a count made on the day of onset of the symptoms. In these cases the leukocyte count was :

Above 20,000	in	2 cases.
Between 15,000 and 20,000	"	1 case.
" 10,000 and 15,000	"	1 "
" 9,000 and 10,000	"	1 "
" 7,000 and 8,000	"	2 cases.
" 6,000 and 7,000	"	1 case.

In connection with these blood counts it should be remembered that, in every instance but one, the phlebitis came on in the third week of the disease, or later, at a period when, according to our statistics, the leukocyte count in uncomplicated cases should not be above 5500.

Association with Secondary Infections. Out of our 39 cases there were 7 instances in which secondary infections had preceded or coexisted with the onset of the thrombosis. These secondary processes were:

Boils	in 2 cases.
Well-marked bronchitis	" 1 case.
Gangrene of the lung	" 1 "
Fistula in ano	" 1 "
Chronic otitis media	" 1 "
Amœbic dysentery with developing hepatic abscess	" 1 "

In the remaining 32 instances there was no clinical evidence of secondary infection.

Postmortem Appearances. In the three instances in which bits of the clogged vein were examined histologically evidences of well-marked inflammatory changes were found in the walls of the vessels—such, however, as might well have arisen secondarily to the thrombosis. In one of these cases there was, at the point of section, an extensive endophlebitic plaque which, however, probably dated from a period preceding the typhoid fever. The sections examined came from a spot above the point of origin of the thrombus. There was nothing in the sections which would justify one in drawing conclusions as to the cause of the thrombosis or as to the pre-existence of a phlebitis.

Cultures. In one case the *bacillus typhosus* was obtained in pure culture from the thrombus. In one the cultures were negative. No notes were made with regard to cultures from the thrombus in the other cases which came to autopsy.

After Results. Sixteen patients were seen or communicated with at periods, months or years after the onset of the complication; 10 of these were cases of femoral thrombosis; 2 of double iliac thrombosis; 2 of popliteal thrombosis; 2 of thrombosis of the deep veins of the calf.

(*a*) *After History of Ten Cases of Femoral Thrombosis.* One patient was seen two and one-half months after convalescence; one ten days after his discharge from the hospital, while two of the others were communicated with a year after the onset by letter. The other six patients were examined at periods varying from two to twelve years after their illness.

In all instances there was more or less permanent disability. In 6 cases there had been *œdema*, lasting for from several weeks to two years.

In 5 cases there was a complaint of *cramps* in the calves, especially at night and after exercise.

In 1 the patient complained of sharp *pains* running up through the leg and thigh, especially after standing.

In 1 instance the patient says that when he uses his leg too much "it becomes so weak that he can hardly move it; it seems to give out."

In every instance the affected leg and thigh were materially and permanently *larger* than the other.

In all cases, excepting in the instance seen ten days after discharge, there were marked *varices*. These were especially extensive in the calf, the popliteal space and on the posterior and inner side of the thigh. In 6 cases, all but 1 in which the condition was looked for, there was well-marked varicosity of the veins in the hypogastrium. These seem to be characteristic. The dilated veins form a triangle with the apex a little below the umbilicus, the blood flowing from the affected thigh to the apex of the triangle, and then down again into the inguinal ring on the other side, passing upward, evidently through the opposite iliac vein.

(*b*) *After History of Two Cases of Double Iliac Thrombosis.* Two patients who had had a double iliac thrombosis were seen several years after the onset of the complication. In one of these instances there was at first much œdema and persistent weakness of the legs. In the other there were few subjective symptoms. In both cases there were most extensive varicosities on both legs and thighs extending upward over the abdomen and anastomosing with the internal mammary veins and other veins in the axilla. The plate shows the condition of the more marked of these two cases.

(c) *After History of Two Cases of Popliteal Thrombosis.* Two cases of popliteal thrombosis were seen several years after the onset of the complication. One of these patients had complained of no trouble whatever. In the other the leg was somewhat weak, and toward the end of the day it became at times œdematous. In both instances the affected leg was somewhat larger than the other, but in neither were there marked varicosities.

(d) *After History of Two Cases of Thrombosis of the Veins of the Calf.* In one case there was, after leaving the hospital, considerable œdema with the development of several ulcers. There is now a fairly well-marked varicosity of the veins of the inner side of the leg and in the popliteal space. The other patient was communicated with by letter. He states "that the leg from the knee down is the source of a little continuous annoyance. It itches, and is frequently inflamed during the warm months. It often goes to sleep." The calf measures an inch and a half more than the other.

FINAL OBSERVATIONS. Conclusions based upon so small a series of observations are hardly justified. There are, however, one or two points worth emphasizing:

1. In 42 cases of typhoid thrombosis the onset occurred almost invariably in the third week or later.

2. Local pain and fever were usually the first symptoms. The fever sometimes preceded the localizing symptoms.

3. In 28.2 per cent. of our venous thromboses occurring in connection with typhoid fever there were chills. In several instances the chill preceded the appearance of localizing symptoms. In the past two years I have seen in consultation 3 further cases in which otherwise unaccountable chills during convalescence from typhoid fever were followed by thrombosis.

4. Venous thrombosis in typhoid fever is usually associated with an increase in the number of leukocytes. The extent of the leukocytosis depends apparently in part, at least, upon the extent of the lesion. It may be moderate, but in other instances is of considerable extent—over 20,000. In mild cases it may be absent.

5. The thrombosis is commonest in the lower extremities, espe-

cially on the left side. The femoral vein is involved with particular frequency.

6. In the event of a sudden severe pain in the lower part of the abdomen, coming on during the latter part of typhoid fever, and associated with a leukocytosis, the possibility of iliac thrombosis should always be considered.

7. Venous thrombosis in a lower extremity is always a serious complication of typhoid fever. Although the immediate danger is not great, the after results are often grave.

In thrombosis of the femoral or iliac veins the affected extremity is usually permanently and considerably enlarged, and there is usually more or less persistent disability—extensive varices often resulting in ulceration; marked weakness of the limb; frequent cramps in the muscles, especially at night and after overexertion.

In thrombosis of the popliteal or deep veins of the calf alone, the permanent changes are much less severe, though the leg always remains larger than the other.

8. In thrombosis of the femoral vein a greater or less part of the blood from the affected extremity is often carried up by the iliac vein of the opposite side, the current crossing the abdomen through anastomoses in the hypogastrium, resulting in a characteristic triangular area of varicose veins.

DISCUSSION.

DR. PEABODY: As bearing upon the etiology of venous thrombosis following typhoid fever, I would like briefly to call attention to a paper published in the last volume of the *Medico-Chirurgical Transactions* by two gentlemen connected with the Army Medical School at Netley, in which they seem to show that it can be contributed to by an accumulation of the calcium salts in the blood. They show experimentally that an increase in the calcium salts in the blood increases the rapidity of coagulation, and draw the conclusion that in typhoid fever this may be brought about by the large amount of milk ingested. They think, also, that it can be checked by giving sodium citrate without doing any harm to the patient.

DR. STENGEL: Dr. Thayer referred to one case of thrombosis of the pulmonary artery, and I presume that is the case reported *in extenso* by Flexner

some years ago. In looking up the literature I found this to be the only well-reported case. I have seen two cases myself lately, and I was interested in the question as to the possibility of primary embolism from an abdominal vein or from the extremities. In my cases I concluded the process was primary thrombosis of the pulmonary artery and in both there was terminal necrosis of the lung. In respect of the symptoms of thrombosis I have seen a number of cases in which there were general symptoms before the local symptoms, such as were referred to by Dr. Thayer. I have in mind one case in particular in which the patient was admitted with a very marked septic condition, the temperature reaching 107° F., very decided chills, and a leukocyte count of 7000, a leukocytosis according to the figures Dr. Thayer has given us. The appearance of the patient led to the suspicion of post-typhoidal thrombosis, and this was proven to be the condition.

DR. WELCH: I think there is a good deal of evidence in these cases in support of the theory that they start with a primary inflammation of the walls of the vein. Of course, this is only a recurrence to a very old notion that was supposed to have been overthrown by Virchow. Such symptoms as Dr. Thayer has drawn attention to in his paper—chills, elevation of temperature and local pain, and another symptom that might be emphasized, the disturbance of the pulse—point to an inflammation of the venous wall, a phlebitis. The French workers have brought this forward recently very forcibly.

Dr. Longcope, in my laboratory, went over the pathological specimens lately, and demonstrated the presence of bacteria on over 70 per cent. of the cases. I think there is much in favor of the view that the thrombosis is due to a localized infection of the vein's walls, and it would be difficult to explain the sequence of phenomena otherwise than that it is a primary infection of the wall. At the same time the question is by no means settled.

DR. PRINCE: It may be interesting, in connection with what Dr. Welch has just said, to report a case of typhoid that began with phlebitis in the leg; as the typhoid developed its diagnosis was masked by the previously existing inflammation. For a time it seemed as if the typhoidal symptoms might be due to some septic process elsewhere, secondary to the phlebitis. It is fair to say that this case was one that had previously had a number of attacks of phlebitis, probably due to a gouty diathesis, and therefore the occurrence with typhoid might have been a coincidence.

DR. CARY: I would like to refer to the marked disproportion between the general systemic symptoms and the local condition. I recall distinctly one case where the local trouble did not seem to be very great, but where the chills were as violent as in the vicious types of malaria. There is one other point referred to by Dr. Thayer that I would like to speak of, and that is that these cases recover entirely of the local œdema.

DR. W. GILMAN THOMPSON: The after-history of these cases, as pointed out by Dr. Thayer, is interesting. I have eight cases that have been under observation from six to ten years, and in not one is there anything like complete recovery. Every one of them, after any prolonged exertion, has to take several days' rest to overcome the œdema that results. One of these patients very closely resembles the photograph that is passing around. He came to me the other day with an attack of appendicitis and had to undergo an operation, and the thrombotic veins seriously complicated the operation.

In regard to the condition of the pulse during the formation of the thrombus, it may undoubtedly be modified at that time, but it has always seemed to me that the force of the circulation has very slight effect in determining the location of the thrombus, for the reason that the thrombi occur usually during or near convalescence, when the pulse is improving and, in fact, is nearly at its best.

DR. TYSON: Dr. Thayer's paper has revived a question that has often occurred to me, viz., the cause of pain in vascular obstruction. It would seem that it matters not whether arteries or veins be obstructed, pain is a constant feature of such obstructions. We have one of the most striking instances in angina pectoris, it being generally conceded that the agonizing pain of this affection is due to obstructions of the coronary artery. It has occurred to me that the pain, often so extreme, accompanying ordinary cramp may be explained similarly.

DR. OSLER: There is an interesting difference between the phlegmasia alba dolens of the puerperium and that of typhoid fever. How rarely one sees the leg so swollen, so hard, and so painful in typhoid thrombosis as in the other? Nor is there often that extreme agonizing pain seen in postpartum cases. The usual experience is scarcely so severe in the after-effects as would appear from our reports. I have known a number of cases in which the recovery has been perfect, and I think our hospital experience is exceptional. As the attending physician is blamed for everything that happens, I always instruct my students to blame the parents of the patient if his leg remains swollen. With proper anastomosing vessels he would not have a swollen leg after a thrombosed femoral vein in typhoid fever.

DR. THAYER. It seems to me that the evidence is decidedly in favor of the idea that these cases of venous thrombosis are for the most part due to a primary phlebitis. I did not especially analyze the pulse in these cases, but in one instance the heart's action was remarkably rapid at the time of the onset of the symptoms.

VARIETIES OF SPLENIC ANEMIA.

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THIS report of five cases, with pathologic studies in three of them, is presented as a contribution to the knowledge of the condition generally designated as splenic anemia. I have elsewhere expressed doubt regarding the individuality of such a condition, and the conviction that many different sorts of diseases have been classed under this name. For convenience of clinical terminology the name may, however, be retained, and perhaps some order may be established before long.

CASE I. *Male, aged fifty-nine years, history of dysentery (?), duration over two years, probably six years or more; stunted growth, pigmented skin, clubbed fingers, osteoarthritis, enlarged spleen; chloroanemia with leukopenia, hemorrhages, diarrhea; early enlargement followed by diminution in the size of the liver; numerous intercurrent infections; death in stupor; autopsy.*—L. C., a cigarmaker, aged fifty-nine years, native of Belgium, was admitted April 18, 1900. The history recorded at that time is as follows: His father died of phthisis, his mother of jaundice, one brother of rheumatism. He had jaundice twenty-two years before and gonorrhea sixteen years before. He denied syphilis and malaria, but had been in Mexico and Africa with the French army and may have had malaria. He gave an uncertain account of some sort of diarrheal disease in Africa, perhaps dysentery. He was married at thirty-two; his wife and two children died of phthisis.

Four and a half years ago noticed a beginning alteration in the skin in the form of patches of pigmentation alternating with light areas. Six or seven months ago had a chill and fever, and this has been repeated at intervals of a few weeks. He complains of a buzzing in his ears and of a scaly, itchy eruption on his legs, During the last two months has grown weak and dyspneic.

Status Præsens. The patient is a somewhat undersized man. There is a bronze discoloration of legs and arms, and, to a less extent, of abdomen and

chest, with areas of lighter color between. In places on the abdomen the skin in the bronzed areas is desquamating, leaving normal-colored skin beneath. The fingers are markedly clubbed. Patches of dermatitis are found on both ankles, and there is slight edema. The liver extends from the fifth rib to within an inch of the umbilical level. The spleen extends from the eighth rib to an inch below the anterior superior spine of the ilium. Two marked notches can be felt in the anterior border. Scattered rales are heard in the lungs; a systolic murmur and an accentuated second sound at the aortic interspace. Otherwise normal physical signs are obtained (Figs. 1 and 2).

April 18, 1900. Blood examination: Red blood corpuscles, 3,520,000; hemoglobin, 51 per cent.; white blood corpuscles, 5280.

May 1st. Blood examination: Red blood corpuscles, 3,630,000; hemoglobin, 76 per cent.; white blood corpuscles, 2600. (The first hemoglobin estimate was thought erroneous at the time.) Differential count: Polymorphonuclear, 68.9 per cent.; mononuclear, 1.9 per cent.; transitional, 4.9 per cent.; lymphocytes, 22.6 per cent.; eosinophiles, 1.4 per cent.

Urine Examination. Specific gravity, 1010; acid; no albumin; no sugar; microscopically negative.

6th. The patient had a chill, followed by fever, delirium and cellulitis of right leg, which finally required incision for the removal of a small amount of pus. The leukocytes numbered 6120; the blood was examined for malarial organisms at the time of this chill, and repeatedly later, but none were found. The cellulitis seemed the result of scratching one of the eczematous patches on the ankle.

June 5th. Slight jaundice, no change in liver, no fever.

13th. Right-sided orchitis; edema of right leg.

14th. Chill; temperature, $104\frac{3}{5}$; impairment and rales at right base.

21st. Still impairment at right base.

24th. Blood: Red blood corpuscles, 3,560,000; hemoglobin, 46 per cent.; white blood corpuscles, 2760.

July 3d. Considerable hemorrhage for several days, due to extraction of a tooth.

August 9th. Continuance of slight jaundice; also occasional elevations of temperature. No bile in urine.

September 11th. Marked pharyngitis.

October 17th. Periodic neuralgia in various parts of the body of late.

November 2d. Spleen seems a little smaller; liver certainly smaller.

9th. Definite neuritis. Arsenical treatment suspended. Improvement on discontinuing the drug. Pigmentation more marked of late.

26th. Another attack of lymphangitis of right leg. Inguinal glands at saphenous opening enlarged. The attack began with chill and fever. Blood examination: Red blood corpuscles, 3, 710,000; hemoglobin, 74 per cent.; white blood corpuscles, 4160.

December 17*th*. Another attack of right-sided orchitis.

January 7, 1901. Diarrhea.

17*th*. Considerable hemorrhage after extraction of a tooth.

February 17*th*. Chill; temperature, 101°; facial erysipelas.

March 4*th*. Pain in right elbow.

19*th*. Marked pharyngitis and laryngitis. Some impairment of resonance in right chest. Mucopurulent blood-streaked sputa. No tubercle bacilli. Daily fever in afternoon. Blood: Red blood corpuscles, 4,670,000; hemoglobin, 60 per cent.; white blood corpuscles, 1920.

May 8*th*. Another attack of right orchitis.

June 10*th*. Recently complains of pain in region of spleen.

16*th*. Much pain in right arm.

July 8*th*. Marked diarrhea. Blood: Red blood corpuscles, 2,950,000; hemoglobin, 45 per cent.; white blood corpuscles, 2720.

October 15*th*. Liver smaller, lower border only two fingers' breadth below costal margin. Hair growing very white. Pain in right arm continues.

22*d*. Blood: Red blood corpuscles, 4,060,000; hemoglobin, 61 per cent.; white blood corpuscles, 2460. Differential count: Polymorphonuclear, 78 per cent.; mononuclear, 6.52 per cent.; transitional, 6.5 per cent.; lymphocytes, 6.5 per cent.; eosinophiles, 2.5 per cent.

November 11*th*. Thickening about right elbow-joint.

February 5, 1902. Blood and mucus from bowel. Fistula discovered.

March 4*th*. Increased diarrhea. Patient's strength failing greatly. Blood: Red blood corpuscles, 3,160,000; hemoglobin, 64 per cent.; white blood corpuscles, 10,600.

8*th*. Blood: Red blood corpuscles, 3,890,000; hemoglobin, 68 per cent.; white blood corpuscles, 11,040. Unconscious and restless during night; died in stupor.

Autopsy. (Dr. Hendrickson, pathologist.)

Pathological Diagnosis. Pigmentation of skin and jaundice; chronic splenic tumor; atrophic cirrhosis of liver; acute lobar pneumonia; chronic interstitial orchitis; arteriosclerosis of aorta; chronic arthritis of right radiohumeral joint.

Detailed Description of the Organs. External Appearance. Body that of an extremely emaciated and poorly developed white male. Mucous membrane pale; rigor mortis absent; no edema; considerable postmortem lividity of dependent portions. Over sacrum is discovered a small bed-sore about 3 cm. in diameter and superficial in character. There is marked jaundice with a brownish pigmentation of the skin. The distribution of the pigment is confined entirely to the extremities. It is found over lower extremities below the knees in large, irregular patches, which are more or less confluent; the intervening areas of skin are of normal appearance. The same pigmentation is found over the hands and forearms. Fingers show marked clubbing. Superficial lymph nodes not enlarged.

FIG. 1.

FIG. 2.

FIG. 3.

Coarse hematogenous pigment masses surrounded by fibrous tissue.

FIG. 4.

Section of liver. × 41.6.

Abdominal Cavity. Spleen is found enlarged and projects about 6 cm. below the costal margin. Upper border firmly adherent to the under surface of diaphragm. Liver does not extend below the costal margin except in the epigastric spaces, where it projects 3 or 4 cm. below the xiphoid process. Otherwise cavity negative. Mesenteric lymph nodes not enlarged.

Pleural Cavities. Negative.

Pericardial Cavity. Negative.

Heart. Weight, 270 grams; normal except myocardium, which is paler than it should be.

Lungs. Left: Surface dark red in color, but everywhere smooth. On section cut surface dark red, and from the cut vessels considerable blood flows. Consistency considerably increased, and on pressure a marked amount of dark, bloody fluid and air escape. The condition is uniform from apex to base. Bronchial lymph nodes deeply pigmented, but not enlarged. Right: Surface dark red and smooth. No evidence of pleurisy. On section the lower lobe and small portion of the upper lobe are found consolidated. This part of lung is grayish-red in color, and on pressure a small amount of puriform fluid can be expressed. Middle lobe and upper portion of upper lobe are not so firm in consistency, but show marked congestion. Bronchial lymph nodes also pigmented, but not enlarged.

Spleen. Weight, 950 grams; considerably increased in size. Except where adherent to diaphragm, surface smooth. On section, capsule slightly thickened; trabeculæ prominent; pulp increased in amount and dark red in color. Malpighian bodies not visible. Consistency of the organ decreased.

Gastrointestinal Tract. Normal except at lower portion of rectum, where the mucous membrane shows marked swelling and congestion of the bloodvessels.

Pancreas. Normal.

Liver. Considerably decreased in size; surface roughly lobulated, giving rise to a typical hobnail surface. Over the anterior surface of the right lobe is found an irregular-shaped area of depression about 4 cm. in diameter, which, however, shows no thickening of Glisson's capsule. Also along the free border near the gall-bladder there is an area of depression. Section through these areas shows no scars in the depth. General appearance of cut surface is dark brownish-red, but liver tissue is divided into large areas of varying size by connective tissue. Consistency of liver distinctly increased. Gall-bladder normal.

Adrenals. Normal.

Kidneys. Of normal size; capsule strips readily; surface grayish-red in color. Weight of kidneys, 300 grams. No injection of stellate veins. Cut surface shows moderate congestion of bloodvessels, but otherwise no visible change.

Bladder and Ureter. Normal.

Prostate. Normal.

Testicle. Left, normal; right, slightly decreased in size. Slight increase in thickness of its surrounding coats. Throughout the gland proper is discovered

a marked increase in grayish, firm connective tissue. Tubules do not pull out as readily from this gland as from the left.

Aorta. Shows a few scattered patches of sclerosis. None of the lymphatic glands show increase in size.

Bone-marrow. From shaft of femur is dark grayish-red in color, and of firm consistency.

Organs of Neck. Marked congestion of bloodvessels of mucous membrane over larynx and trachea. Considerable mucus in trachea. Right thyroid lobe slightly increased in size. On section, however, nothing abnormal can be discovered.

Spinal Cord. Examination without sectioning shows nothing abnormal.

Right radiohumeral joint removed *in toto.* Examination of the interior of this joint shows a superficial erosion of cartilage and bone over a small portion of the prominence separating the radial articular surface from adjacent bone. Also a more marked erosion of the articular surface in the greater sigmoid cavity of the ulna.

Microscopic Features. (Examination by Dr. Stengel.) *The Spleen.* There was throughout this organ a diffuse connective-tissue hyperplasia involving the walls of bloodvessels, the trabeculæ of the organ, the splenic pulp and the Malpighian bodies. Throughout the pulp this process was diffuse and cellular, but in and around the Malpighian bodies and elsewhere in circumscribed foci it was of a denser nature with a marked tendency to hyaline change. In a number of places a peculiar form of pigmentary deposit was observed within areas of dense fibroid tissue. In such areas brownish pigment masses of a hyaline or almost crystalline appearance were found within a focus of dense connective tissue. Stained with ferrocyanide of potash and muriatic acid these formations gave a distinct iron reaction, which, with the general appearances, showed the pigmentation to be of hemorrhagic origin. The coarse character of these lesions and the marked connective-tissue change around them gave a peculiar appearance that I have not seen in any other spleen, excepting from one other case of similar clinical character (Fig. 3).

The connective-tissue growth in the walls of bloodvessels and surrounding them was very pronounced, and many of the smaller vessels were entirely obliterated.

In the splenic pulp many pigment cells containing rather coarse, brownish pigment were found, quite apart from the areas of marked pigmentation before referred to. Everywhere throughout the spleen there were foci of recent hemorrhage, sometimes side by side with older hemorrhagic pigmentation, and sometimes independent of such. Altogether there were decided evidences of congestion and hemorrhagic processes of old and recent origin, with secondary fibroid and pigmentary changes. Independent of these the substance of the organ presented a diffuse fibroid change of seemingly irritative character. Under higher powers swollen and proliferated endothelial cells were moderately

conspicuous in the sinuses, but nowhere were these aggregated to form distinct masses.

The Malpighian bodies were extensively altered. Many had become converted into fibrous and hyaline masses; others were partially affected by fibrous change beginning around the central vessel; only a few were found without some alteration of structure.

The Liver. There was a very pronounced grade of connective-tissue infiltration of interlobular and intralobular character. In many places the hepatic lobules were surrounded by a dense cellular connective-tissue growth which was most markedly interlobular, but also invaded the atrophied lobules. The liver cells themselves were moderately pigmented, but were quite generally distorted and atrophied. The portal veins were widely distended, but the central vessels of the lobules were narrowly contracted and nearly free of blood (Fig. 4).

The Lymphatic Glands. All of the lymphatic glands showed diffuse, fibrous change of moderate character, and intense congestion with widely dilated blood spaces. The glands from various portions were not examined with reference to the distinctive changes in the different groups.

The Bone-marrow. The marrow from the shaft of the femur showed distinct lymphoid characters. The majority of the cells were large and small neutrophile myelocytes, with pale, eccentric nuclei. Eosinophile myelocytes were present in small numbers, and rather more eosinophile cells of the ordinary type. Pale hemoglobin-containing cells of doubtful nature observed, but no distinct nucleated red corpuscles. Polymorphonuclear and fat cells were not numerous.

Other Organs. The sections of the lung showed decided fibroid and cellular pneumonia. There was undoubtedly an old fibroid process with more recent bronchopneumonia. The pancreas and kidney showed moderate sclerotic change. The right testicle was markedly altered, being practically converted into fibrous tissue. Several areas of hemorrhagic pigmentation, similar to the coarse pigmentations in the spleen, were found in the testicle.

CASE II. *Female, aged two years and eight months. Enterocolitis at one year; little evidence of rickets; pallor, enlarged spleen, palpable superficial lymph glands; severe anemia, at first without, later with, leukocytosis; diarrhea, terminal tuberculosis and endocarditis; duration one and a half years; autopsy.* Elsie S., aged two years and eight months; admitted October 13, 1899.

Family History. Both parents and two sisters are living and in good health.

Previous History. One year before had a severe attack of enterocolitis. The child was healthy with this exception until the present illness. Began to walk when twelve months old (Fig. 5).

Present illness began when she was twenty months old. The parents first noticed increasing size of the abdomen and pallor.

Status Præsens. Ashy pallor; slight osseous signs of rickets; abdomen large and globose, quite tense. Enlarged spleen, with notches easily palpable. Liver enlarged to percussion, but edge cannot be felt. No fluid in abdomen.

All superficial lymph glands enlarged and easily palpable. Heart is found under sternum, extending an equal distance to right and left. A short systolic, puffing murmur is heard at the left side of cardiac dulness. Breath sounds harsh, but resonance good.

Blood Examination. Red blood corpuscles, 2,920,000; hemoglobin, 30 per cent.; white blood corpuscles, 7600. Differential count: Polymorphonuclear, 50 per cent.; mononuclear, 17 per cent.; lymphocytes, 31 per cent.; eosinophiles, 1.6 per cent.; myelocytes, 0.4 per cent.

There was constant diarrhea, the movements numbering from three to five daily.

October 25, 1899. The condition continues without much change. The skin has become somewhat yellowish. At this date the spleen extends a finger's breadth below the anterior superior spine of the ilium, and the anterior edge is within one-half inch of the middle line. The liver is still enlarged to percussion, but the edge cannot be felt.

The heart is now in a more normal position, extending from the third rib above to the sixth below and from left nipple line to right border of sternum. The same soft, systolic murmur is heard, but it is not transmitted beyond the cardiac borders. The point of maximum intensity is at the pulmonary region. The second pulmonary sound is not accented.

The left kidney can be plainly felt in the back, being seemingly pushed backward; the right is less plainly felt.

26*th.* Several small masses can be felt in the abdomen. They seem to disappear after a movement of scybalous masses.

November 4*th.* The submaxillary, submental and cervical glands are distinctly enlarged.

15*th.* Moderate fever and continued diarrhea.

December 8*th.* General urticaria followed by swelling of eyelids, face, legs and arms.

10*th.* The swelling has disappeared.

11*th.* Blood: Red blood corpuscles, 3,920,000; hemoglobin, 40 per cent.; white blood corpuscles, 14,720. Differential count: Polymorphonuclear, 49.2 per cent.; mononuclear, 2.4 per cent.; transitional, 12.8 per cent.; lymphocytes, 34 per cent.; eosinophiles, 1.6 per cent. Polychromatophilia; a considerable number of normoblasts.

16*th.* Physical signs the same, but liver seemingly larger. Edge can be felt. Kidneys still easily palpable in flanks.

January 27, 1900. Has been better of late. Now a greenish-yellow pallor is noted.

February 15*th.* Sudden fever, with scarlet flush of face and neck; later, papules which were bright red at first, but soon faded.

The later notes have been unfortunately mislaid; but the final phase was one apparently of disseminated pneumonia with continued fever of about

103° to 104°; respirations varying from 50 to 68, and corresponding pulse rate.

(The autopsy was made by Dr. Flexner).

Pathologic Diagnosis. General lymphatic enlargement, with congestion and hemorrhage of the glands; splenic tumor, with infarctions; anemia of the organs; subacute, vegetative, mitral endocarditis; necrosis of the mucous membrane of the esophagus; tuberculosis of the lymphatic glands and tuberculosis of the lungs; infarction of kidneys.

Bacteriologic Diagnosis. Staphylococcus aureus from heart's blood; aortic valves; esophagus; lungs.

External Appearance. Body of an emaciated, very pale child. Length 82½ cm. The abdomen is much distended. No evidence of fluid. The spleen can easily be felt in the left hypochondriac region. Its lowest border is 21 cm. in the midaxillary line below the ribs. The circumference of the abdomen below the ribs is 47½ cm., and just above the umbilicus 43½ cm. There is a very small amount of subcutaneous fat; indeed, it is in most places absent. There is very slight edema of the lower borders of the ribs. Over the extremities, particularly the lower extremities, are minute, petechial hemorrhages. Over the abdomen are several pigmented depressions, which are probably the remains of small furuncles. No rigor mortis.

Abdominal Cavity and Peritoneum. Upon opening the abdominal cavity the omentum is seen to be adherent to the greatly enlarged spleen. Upon being stripped back, which can be done in part only on account of the old adhesions, it is found that there is a fresh exudate of yellow fibrin over the upper part of the enlarged organ. In the lower border there is an infarction about 2 cm. in width. The surface of the spleen is mottled, the predominating color being brown, and lighter areas corresponding to other infarctions can be seen on its superficial surface. There are no adhesions, excepting to the diaphragm on the upper edge, with the exception of those to the omentum, as already described. The spleen weighs 465 grams. Its measurements are 17 x 9 x 5 cm. Its consistence is firm and even very hard. On section the infarctions described are found to be on the anterior surface; they are three or four in number, varying from 1½ to 3 cm. in their widest portion. They are either anemic or mixed in character. The mixed ones show a cortical anemic layer and a deep brownish-red, rather soft, central portion. They extend about 2 cm. into the substance of the organ. In other portions the spleen is of a reddish-brown color, and there is no distinction of Malpighian corpuscles. Here and there on the cut surface are whitish points about the size of pinheads, which are taken to be small, dense thrombi.

Liver. With the exception of an adhesion on the anterior surface of the right lobe to the abdominal wall, measuring 1½ cm. in diameter, and very old in nature, it is free from adhesions. Its weight is 600 grams. Its cut section is cloudy. Its consistence is not increased.

Kidneys are alike. The capsule strips off easily, showing in each organ a recent infarction about 4 cm. in diameter in the cortex, about which the tissues are greatly congested or hemorrhagic. On section the cortex is pale, pyramids somewhat more injected. Beneath the mucous membrane of the pelvis there is a reddish accumulation which looks like tissue, or may be hemorrhage. Adrenal glands appear normal.

Heart and Pericardium. Pericardial cavity contains about 30 c.c. of clear, yellow fluid. The layers of the serosa are smooth. The right ventricle is dilated. The left ventricle is contracted. The heart's flesh is pale. The tricuspid, pulmonary and aortic valve segments are delicate. The mitral segments are covered with vegetations, quite adherent, which average in size about a bird-shot, some being larger, and as large as a hemp-seed. The two edges of the valve are rather difficult to separate, but this union is due probably to a small clot formed postmortem over the edge. In the diaphragm there are scattered whitish points, probably tubercles.

Lungs. The right lung is bound over the upper portion of the upper lobe to the chest wall. The left lung is bound over the apex to the chest wall. There is no fluid in the pleural cavities. The lungs are insufflated. On section the upper lobes contain disseminated gray tubercles; fewer in the lower lobes. There are no definite foci of consolidation, although in the pleura over each upper lobe are small hemorrhages. Beneath the parietal pleura on the left side, and following the intercostal muscles, are found white or caseous areas of tuberculosis. In the bifurcation of the trachea there is a large gland the size of a pigeon's egg, which upon section is completely caseous.

Stomach and Intestines. The stomach shows nothing of special interest. Postmortem digestion. The duodenum contains a number of elevated, swollen, solitary follicles, after which there is no swelling of any of the follicles throughout the length of this intestine. In the lower part Peyer's patches are visible, but nothing more. The mucous membrane of the large intestine is attenuated. In general, the intestine is thin and apparently atrophic.

Tonsils. Enlarged, and there are irregular depressions. No definite foci can be made out. In the upper part of the esophagus, on a line with the upper part of the thyroid cartilage, there are two foci of necrosis, each about 4 mm. in width, over which there is a dirty-white exudate.

Lymphatic Glands. The inguinal, axillary and cervical glands can easily be made out by palpation. The glands of the neck cause the tissue on each side to project. All the lymphatic glands of the body, upon examination, are found to be enlarged and to be very red in color. The greatest enlargement is found in the cervical and in the inguinal regions, in both of which places the superficial as well as the deep sets are swollen. The swelling affects the individual glands and not the invading tissue. In the cervical region the largest gland is about the size of a pigeon's egg. Most of them vary from a pea to a cherry in size. In the inguinal region the largest is about the size of an almond. The

retroperitoneal glands form chains and large, red bodies. The mesenteric glands and the glands in the mesocolon and the omentum are all enlarged and congested or hemorrhagic. The glands about the pancreas are especially enlarged. Some of them contain whitish nodules, evidently tubercles. The largest of the mesenteric glands contain also a white area, suggesting tuberculous caseation.

Bone-marrow. The bone-marrow of the femur is abundant and red in color. Its consistence is soft.

Microscopic Features. (Dr. Stengel.) The sections of the spleen varied considerably in their appearances according to the part of the organ from which they were taken. Those from the areas of infarction showed only the usual features of dense hemorrhagic infiltration and pigmentation. In other parts the splenic tissue was markedly sclerotic, and sections stained with Biondi's or Van Gieson's stain presented a uniform, rather dense, fibrous reticulum. Hyperplasia of the endothelial cells of the sinus was evident in some places, and large (swollen) endothelial cells of rounded or irregular shape, with one or a few pale nuclei, were found scattered through the spaces. In a few areas groups of such cells were seen lying together. The proper splenic pulp and the Malpighian bodies had undergone an evident atrophy, and many of the latter were converted into hyaline material. A few doubtful miliary tubercles were seen in the sections. These consisted of a small giant cell surrounded by a group of round (lymphoid) cells. There was no evidence of necrosis.

Lymphatic Glands. The sections of mesenteric lymph glands showed marked thickening of the capsules and of the trabeculæ, the latter separating the lymph follicles in an unusually marked manner. The medullary part of the glands was occupied by numerous widely distended blood spaces or vessels. The lymphoid tissues proper showed no special alteration, but decided proliferation of endothelial cells of the sinuses was seen in places, and numerous macrophages containing one, two, three or more erythrocytes or fragments of such were found. The red corpuscles within the lymph sinuses were much broken, and everywhere fragments of irregular or more commonly rounded shape, and with distinct basic staining reaction, were found among the degenerated erythrocytes. These fragments were of precisely the appearance of blood plaques, and from their situation and general character could be plainly recognized as derivatives of degenerated red corpuscles.

The Liver. Marked lymphoidal and leukocytic infiltration between the columns of liver cells was the most striking feature of the sections as seen under a low form. In areas there was distinct interlobular fibrosis surrounding the portal vessels. The latter were considerably dilated and, besides containing fragmented and degenerated red corpuscles as well as normal erythrocytes and leukocytes, in many places also contained numerous plaque-like formations such as have been described for the lymphatic glands. Here and there in the dilated portal vessels could be found large endothelial cells of the same appear-

ance as those of the spleen and lymphatic glands. These were distinguishable from the lining endothelium of the bloodvessels of the liver, and if derived from this source had manifestly undergone secondary change. No such cells could be found outside of the bloodvessels. They were too numerous and widespread to be attributed to accident or artefact.

The Lung. The lung tissue in general showed no marked alterations in the sections examined, but a few peribronchial miliary tubercles were seen in portions especially selected to determine the nature of the gray bodies observed at the autopsy.

The Bone-marrow. Unfortunately the material was lost and microscopic examination could not be made.

CASE III. *Female, aged twenty-one years, married, two stillborn children; probable onset years before; enlarged spleen, palpable superficial lymph glands, pain in left side, slight anemia, splenectomy; postoperative pneumonia; recovery; histologic examination of spleen.*—Annie D., aged twenty-one years, negro; lived in North Carolina until a year ago, when she came to Philadelphia. Had two stillborn children about a year ago. Her father died of malaria, her mother of an accident. No brothers or sisters. The patient has always been in good health; menses always regular and normal. She says that for many years there has been more or less pain in the left side of the abdomen. She cannot tell exactly how long this has been. Until three months ago the pain was not, however, severe enough to keep her from attending to her usual duties, but during the last three months it has been so severe at times as to compel her to take to bed. During the same length of time she has noticed a lump in the left upper abdominal quadrant. The pain is dull and aching in character, but becomes more severe when the patient moves about. There has been some loss of weight during the last three months.

Status Præsens. The patient is fairly well nourished, looking somewhat older than her years. There is nothing striking on external examination excepting a projection in the left upper half of the abdomen. The superficial lymphatic glands, cervical, axillary, inguinal and epitrochlear are all palpable. Heart and lungs normal. Occasionally a short systolic murmur was heard over the root of the pulmonary artery.

Abdomen. There is marked prominence of the left side above. This moves downward on full inspiration. On palpation a greatly enlarged spleen could be palpated and was distinguishable by the notches in front. At first palpation was somewhat difficult on account of tenderness, but later the patient seemed to be suffering less pain. The mass extended downward and forward to within an inch and a half of the linea alba at the level of the umbilicus, and to about the level of the crest of the ilium below. The posterior border is felt as a thick, rounded surface, while the anterior border has a fairly sharp edge with a distinct notch. No nodules or irregularities can be felt along the edge above the ribs. The mass extended to the sixth rib.

FIG. 5.

FIG. 6.

Spleen. × ½

The liver extended from the sixth rib to the edge of the ribs. It was not palpable. The stomach was crowded upward and forward, as could be determined by inflation, and the colon was pushed downward.

Blood. Red blood corpuscles, 4,440,000; white blood corpuscles, 5600; hemoglobin, 70 per cent. The stained specimens show a slight reduction in the color of the red blood corpuscles, but no other peculiarities were discovered. Degenerative changes, such as polychromatophilia and basic degeneration, were wanting. The differential count of the leukocytes at this time showed no marked peculiarities, though the count has been lost.

Urine. Specific gravity, 1020; amber color, acid, no albumin, no sugar. Microscopically granular precipitate, epithelial cells and a few leukocytes were found.

The patient was kept under observation for some weeks, during which the condition remained practically unchanged. There was apparently no increase in the size of the spleen and no change in the patient's general condition excepting, perhaps, a decrease in the amount of pain. Her weight remained exactly the same. It was decided that the case was one of splenomegaly, and that, on account of the pain and incapacity of the patient, operation was desirable. For this purpose she was returned to the service of Dr. John G. Clark, who originally had referred her to me, and who has kindly permitted me to report the case.

On the day preceding the operation the differential count showed the following figures: Lymphocytes, 29 per cent.; mononuclear, 7.4 per cent.; transitional, 5.4 per cent.; polymorphonuclear, 50 per cent.; eosinophiles, 7.8 per cent.; basophiles, 0.4 per cent. The subsequent leukocytic counts following the operation will be seen in the following table:

Date.	Red blood corpuscles.	Hemoglobin.	Leukocytes. Total count.	Lymphocytes.		Mononuclear.		Transitional.		Polymorphonuclear.		Eosinophile.		Basophile.	
				%	No.	%	No	%	No.	%	No.	%	No.	%	No.
Jan. 1, 1904	.....	.....	5,600												
" 27, "	.....	.....	.....	29.0	.....	7.4	.....	5.4	.....	50.0	.....	7.8	.....	0.4	
" 29, "	.....	.....	.....	5.0	.....	4.2	.....	4.0	.....	86.5	.....	0.2			
" 30, "	3,750,000	55 %	35,000	3.0	1050	4.4	1540	7.6	2660	84.8	29,680	.....	.....	0.2	70
" 31, "	.....	62 %	15,640	5.0	832	2.5	416	10.2	1697	74.4	12,380	3.6	599	0.5	83
Feb. 1, "	3,350,000	.....	12,720	3.4	432	2.4	305	8.2	1043	74 8	9,514	10.5	1335	0.3	38
" 2, "	.....	.....	21,120												
" 3, "	.....	.....	21,760												
" 4, "	4,190,000	55 %	17,680												
" 6, "	.....	.....	21,120												
" 10, "	.....	.....	20,000	6.6	1320	2.2	440	7.8	1560	81.0	16,200	2.4	480		
" 14, "	3,840,000	.....	21,520												
" 16, "	.....	.....	23,860												
" 18, "	.....	.....	9,600	9.0	864	2.6	250	9.6	921	70.7	6,787	7.9	758	0.2	19
" 24, "	.....	.....	9,000												
Mar. 14, "	4,080,000	55 %	9,120												
May 5, "	4,900,000	55 %	7,280	18.6	1354	2.8	204	5.7	415	61.9	4,506	11.0	800		

The operation of splenectomy was performed by Dr. Clark on January 28, 1904. The following notes were recorded at the time: The spleen was rather dense in consistency and the surface showed numerous nodules about 1 to 2 cm. in diameter, with depressed centers. The relations of the organs were found as described in the physical examination. There were a few adhesions posteriorly and some in front between the lower border of the tumor and the great omentum. These were tied off; the others gave no trouble. The splenic vessels were ligated with some difficulty on account of the very narrow space between the tail of the pancreas, the cardiac end of the stomach, and the spleen. The liver was slightly enlarged and showed a number of scar-like depressions on the surface of both lobes.

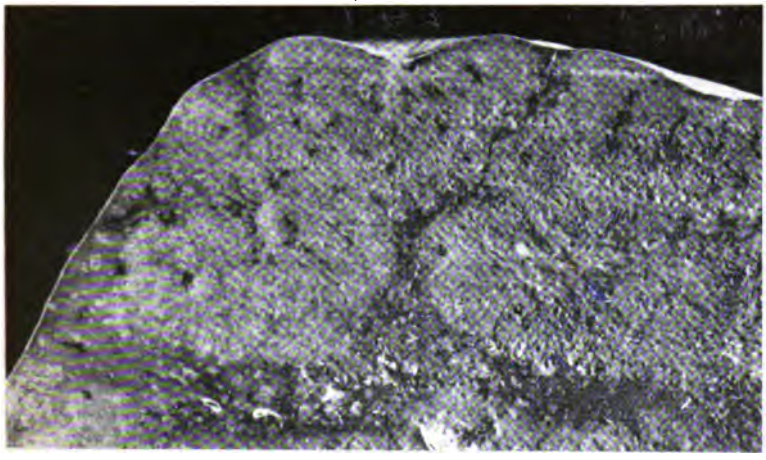
Almost immediately after the operation the patient complained of pain at the base of the left chest and in the left upper part of the abdomen. The temperature rose to 102°, and subsequently kept constantly above normal. At first physical examination was difficult because of the impossibility of turning the patient, but indefinite rales or friction sounds were heard. Later decided signs of a lobar pneumonia were detected. Before this time, however, the upper angle of the incision was opened in the effort to discover the cause of the pyrexia, and a small area of induration, but no suppuration, was discovered. On February 17th, twenty days after the operation, and after the first elevation of temperature, the fever subsided by crisis, going from 103° to the normal in the course of a few hours, and remaining normal continuously thereafter. At the same time the leukocytes declined from over 20,000 to 9600, and subsequently remained normal or subnormal.

After the full recovery from the operation the patient showed no change in appearance or physical signs, excepting those referred to the left upper part of the abdomen. She complained of some dragging and other unpleasant sensations in this region, but as compared with her condition before the operation was certainly much relieved. Three months after the operation I found her in comparatively good health, able to attend to her work as a chambermaid and with practically no local symptoms. The lymphatic glands seemed to have increased somewhat in size, but the difference was not very marked.

Among the interesting features in the blood count of the case was the behavior of the lymphocytes and eosinophile cells. It has been found by experiment, as well as after operative removal of the spleen in man, that there is an increase in the number of lymphocytes and later an increase in the eosinophile cells. The proportion of the latter was at the time of the operation decidedly increased (7.8 per cent.). The lymphocytes were not specially increased (29 per cent.), but the polymorphonuclear cells were actually and relatively reduced in number. This reduction was, however, in favor of the mononuclear and transitional cells, which at this time and subsequently showed conspicuous increase.

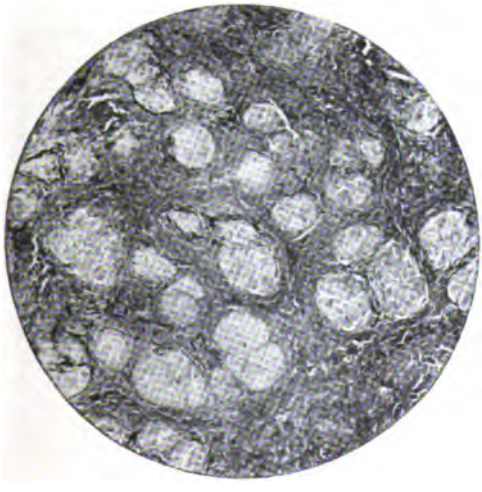
Unfortunately the intervention of an acute pneumonia altered the figures that probably would have been obtained. The result of the postoperative pneu-

FIG. 7.



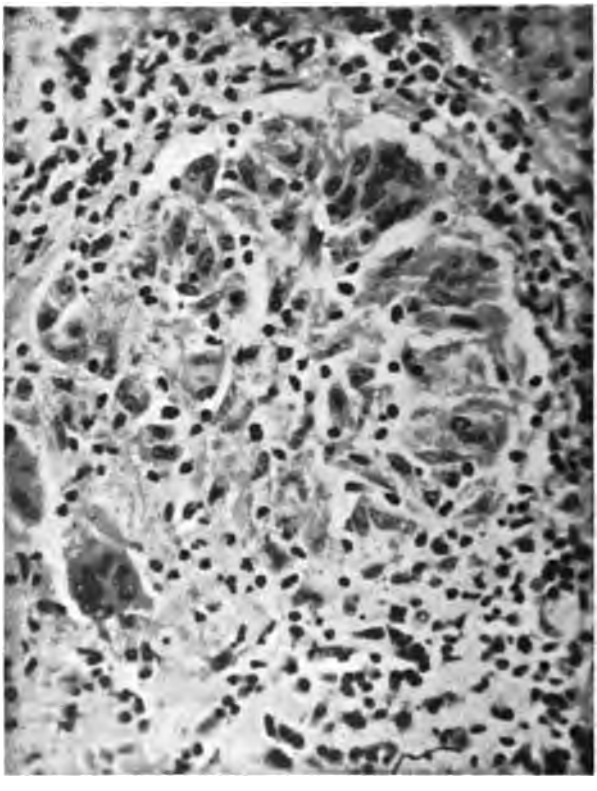
Macroscopic appearance of section (photograph). The lighter areas represent new growth; the darker areas are uninvolved splenic tissue.

FIG. 8.



Microphotograph of section of spleen under low magnification, showing the alveoli containing endothelial cells surrounded by fibrous walls. The photograph exaggerates the density of the fibrous tissue.

FIG. 9.



Microphotograph (high power), showing one of the alveoli containing endothelial cells, giant cells and leukocytes.

monia is the same as is usually seen in normal persons—a marked polymorphonuclear leukocytosis and a reduction of eosinophiles. After the subsidence of the pneumonia there was a return to practically the same conditions as were observed before operation, viz., a marked eosinophilia and reduction of polymorphonuclear in favor of the mononuclear and transitional cells.

Macroscopic Appearance of the Spleen. The organ measured 22 x 13 x 7 cm., and after hardening weighed 1230 grams. The striking features when seen in the fresh state were numerous nodular projections on the surface which presented the appearance of secondary tumors. These varied in size from small masses a half to 1 cm. in diameter up to large nodes fully 2½ or 3 cm. in diameter. The larger nodes were distinctly umbilicated, the depression being quite marked and of a whitish, cicatricial appearance at the bottom. Elsewhere the surface of the organ was red in color, somewhat modified by a more or less thickened capsule. The projecting nodules were numerous anteriorly and on the convex surface of the organ; they were fewer posteriorly and in the hilum. The consistence of the organ as a whole was distinctly increased and was uniform in all portions. On section through its substance practically the entire organ was seen to have been invaded by a growth of a dense consistence and pinkish-red color. This extended inward and toward the hilum, leaving only small parts of the substance of the spleen, which could readily be distinguished by their darker color, uninvolved. Posteriorly and at the hilum the spleen substance was comparatively free. As seen in the cross-section the nodular masses on the surface were manifestly not separate new-growths like secondary tumors, but projecting parts of a large invading mass which occupied the greater part of the organ. The appearance was not unlike such a one as might result from separate pyramidal growths, with the apices projecting from the surface of the organ and extending deeply into the substance, the bases being completely fused or at most leaving small areas of normal splenic tissue here and there between them (Figs. 6 and 7).

Careful examination of the umbilications of the nodules presented no evidence that these had resulted from secondary softening of the centers of the growths, but suggested rather that the elevation surrounding the depressions was the result of an infiltrating process that had not affected the center so that the fibrous tissue of trabeculæ had prevented the elevation at the point of umbilication. Cross-sections showed some excess of fibrous tissue in this central zone, and the cicatricial appearance on the surface was due to thickening of the capsule of the spleen at the point noted, quite as much as to actual fibrous-tissue formation in the center of the nodes. Nowhere in the substance of the new-growth could any evidence of necrosis be discovered by the naked eye, no areas of softening, of caseation, or the like. The tissue was uniform in character, somewhat glistening on section and, as before stated, pinkish-red in color.

Microscopic Appearances. Portions of various parts of the organ were placed in Zenker's fluid, Müller-formol and absolute alcohol, and sections were stained

with eosin-hematoxylin, Van Gieson's stain, Biondi's mixture, carbol-fuchsin, methylene blue, and by Gram's method.

The sections showed a marked new-growth of connective tissue forming alveoli of various sizes (from 0.13 to 0.26 mm. in diameter), and containing large, clear cells, with pale nuclei, and often cells containing several nuclei of the same character. In certain areas giant cells with centrally or eccentrically clustered nuclei were abundant, and everywhere such cells were present, at least in small numbers. The lymphoid elements of the splenic pulp were an inconspicuous feature in all the sections, being crowded into mere zones surrounding the alveolar formations where these were well developed, and being displaced by more diffuse connective-tissue growth in other places.

The alveolar spaces referred to were generally rounded in outline and surrounded by a wall of well-developed connective tissue of considerable thickness. For the most part this wall was compact and separated from the surrounding alveolar or splenic tissue by a sharp line of separation, but elsewhere the transition was more gradual and formed by connective tissue of a less dense character intermixed with lymphoid elements (Figs. 8, 9, 10 and 11).

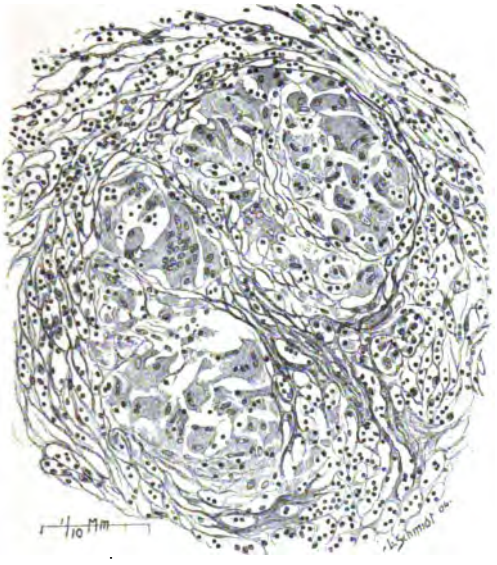
Within the alveoli were found the large endothelial cells before described. In sections through favorable parts of the growth the cells were separate and clearly marked, but more commonly there was an apparent or real confluence making large protoplasmic structures containing large vesicular nuclei. These almost invariably showed nucleoli. Many of the cells contained two or three nuclei. In the peripheral parts of the alveoli, and to a less extent in the center, giant cells with clusters of nuclei were common. The protoplasm of the cells was clear and rather glistening. It did not present any appearance of degeneration, though in some places it was possibly somewhat hyaline. In some of the alveoli, especially those with less well-developed walls, the endothelial cells were separated by or intermixed with erythrocytes or lymphoid cells, but there were no macrophages. Pigmentation was practically absent in this part of the tissue, but was present to a small extent in the reticular connective tissue.

The size of the endothelial cells containing one or two nuclei varied from about 10μ to 20μ in diameter, the average being about 15μ; the size of the giant cells was from 30μ to 72μ, the average of a number being 51μ. The large masses of fused character were even larger, in some places nearly filling the alveolus.

In the portions of the spleen comparatively free from the uniformly infiltrating growth there was still evidence of an active endothelial proliferation, but as the organ was practically entirely involved it cannot be determined if this process were simply an extension from the growth proper or an evidence of prior involvement in lesser intensity of a condition that caused complete transformation in the parts that have been designated the growth proper.

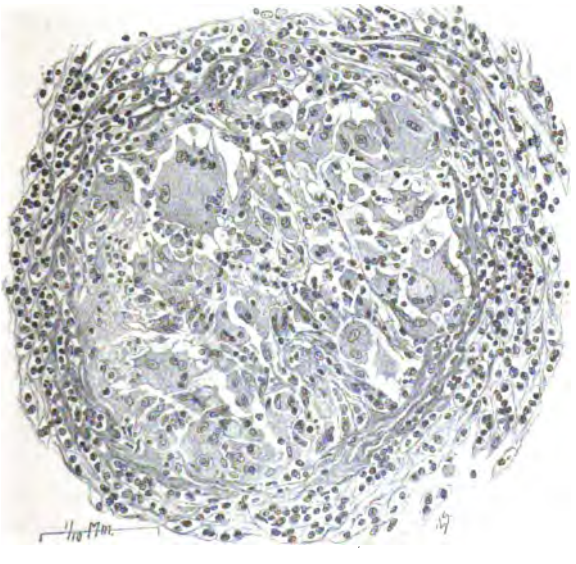
The Malpighian bodies were retained in some places, though atrophied. Elsewhere they were converted into connective tissue or had become hyaline. This, however, was an inconspicuous feature. In general the endothelial

FIG. 10.



Section of spleen. Biondi's stain. × 142.5.

FIG. 11.



Section of spleen. Mallory's stain. × 157.

Fig. 12.

and fibrotic process had simply caused a disappearance of normal splenic features.

In sections from one part of the spleen the Malpighian bodies were conspicuously involved, being occupied by a rounded, acinus-like area of endothelial proliferation, lying adjacent to the bloodvessel of the Malpighian body and sometimes pushing the vessel to one side, but never involving it. In some parts the area of endothelial character was minute; elsewhere almost the whole Malpighian body was transformed. There was no evidence of fibrous-tissue formation in these areas.

Sections stained with carbol-fuchsin and Gabbett's solution showed *no tubercle bacilli*, and those stained by Gram's method likewise showed no bacteria of any kind.

CASE IV. *Man, aged fifty-one years; history of malaria, stunted growth, pigmented skin, clubbed fingers and toes, enlarged abdomen (tympany), enlarged spleen, slightly enlarged liver, moderate anemia, leukopenia, diarrhea, hemorrhages from bowel, rectal ulceration, tendency to chills, no malarial organisms; duration at least three years, probably longer.*—C. T., aged fifty-one years, laborer on railroad, a native of Italy, had come to America six years before. Admitted to Pennsylvania Hospital September 30, 1901.

Family history negative. He himself had had some operation for a mass in the right inguinal region forty years before. During ten years after he was twenty years old he had mild attacks of chills and fever every summer. At thirty-three had some kind of bloody diarrhea for six weeks. Six weeks ago first had pain in the left side of abdomen and distention of the abdomen and diarrhea. The stools were free of blood, but the patient had much rectal pain.

On physical examination the patient was found a small-sized man with darker skin than the average Italian and distinct pigmentation in places. The fingers and toes showed clubbed extremities. The abdomen was enlarged and tense, but did not contain free fluid. The spleen could be felt extending far down into the abdomen. The liver dulness was small in vertical extent. Later the abdominal distention subsided, and the spleen was then found extending to within an inch of the anterior superior spine of the ilium. Rectal examination showed an ulceration in the anterior wall of the rectum (Fig. 12).

Blood Examination. Red blood corpuscles, 4,190,000; hemoglobin, 60 per cent.; white blood corpuscles, 4000.

Urine. Specific gravity, 1012; acid; some albumin present; granular and epithelial casts.

The sputum contains no tubercle bacilli. The feces contain no ameba; the blood serum does not agglutinate Shiga's bacilli.

March 5, 1902. Chill, temperature of $104\frac{1}{5}°$; tongue greatly swollen. Later ulceration under tongue. Leukocytes 11,400. No malarial organisms.

April 1*st*. Admitted to University Hospital. Same conditions noted; also enlargement of practically all superficial lymph glands. Liver extends from

sixth rib to two inches below ribs. Edge easily felt. Spleen as before. A small ventral hernia.

4th. Blood: Red blood corpuscles, 3,980,000; hemoglobin, 70 per cent.; white blood corpuscles, 4400.

10th. Hemorrhage from bowel; diarrhea.

June 6th. Hemorrhage from bowel, about eight ounces; diarrhea.

7th. Considerable hemorrhage from bowel; chills, but no fever.

August 12th. Slight hemorrhage, followed by temperature of 102⅖°, soon normal.

From this date no notable changes. The patient frequently complained of abdominal pain near the umbilicus (ventral hernia), in the left side (spleen), and in the rectum (ulcers). Repeated examinations showed persistence of the ulcers. At intervals he had accessions of cough, with rough breathing and rales. The blood was examined repeatedly and was found in about the same condition as above recorded. Constant diarrhea and frequent hemorrhages were the marked symptoms. The patient was transferred to the Philadelphia Hospital.

This case in its general appearance and in the tendency to repeated infections resembled Case I. very closely. Studies of the blood serum were made to determine if any explanation of the tendency to infection might be found. Dr. J. S. Evans, who conducted these examinations, reported an increase rather than reduction in both immune bodies and complements. The mechanism of the infections must therefore be sought in some other direction.

CASE V. *Woman, aged forty-four years; doubtful history of malaria, enlargement of spleen, succeeded by evidences of hepatic cirrhosis (ascites); no anemia, hydrothorax; duration two and a half years or more.*—Ellen D., aged forty-four years, white, married. Was admitted to the University Hospital November 24, 1903. The following history was recorded:

The patient is a widow and has five children, all of whom are well. She has worked hard all her life.

The family history is negative excepting that one brother died of consumption. No history of new-growths.

Menses began at thirteen years, always normal. Labors normal. The last one eighteen years ago. There was some uterine trouble six years ago, and she was confined to bed for six weeks. She had malaria two years ago, but her description of the symptoms is not very convincing.

About two years ago the patient first noticed some enlargement on the left side of the abdomen. This continued without any local symptoms excepting a slight feeling of fulness and occasionally moderate pain. There has been no loss of weight, but she has become weaker. Her color has at times been a trifle sallow. A little swelling of the feet has recently developed. This comes on during the day and disappears at night. Physical examination showed slight pallor and a subicteric hue of the skin, but no distinct jaundice. Very slight edema of the legs and feet. No cyanosis. Lungs normal, excepting that the

breath sounds appear a little harsh. Heart normal in size; the first sound at the apex is a little lacking in muscular quality, but there are no murmurs. The abdomen is enlarged, especially on the left. The spleen can easily be felt, and on the anterior surface are several distinct notches. The lower border extends below the umbilicus.

The liver extends from the sixth rib to below the costal margin. As the abdomen is generally distended it cannot be plainly felt beneath the ribs, but in the epigastric spaces the edge is distinctly palpable and the substance of the organ is evidently hard and rough. There is decided movable dulness and fluctuation in the peritoneum.

Examination of Blood. Red blood corpuscles, 5,500,000; white blood corpuscles, 8800; hemoglobin, 81 per cent.

Urine. Clear, brownish-red; specific gravity, 1025; no albumin, no sugar; urates, a few leukocytes and epithelial cells.

November 28, 1903. Paracentesis of the peritoneum was performed, and eleven pints and three ounces of clear fluid, yellowish-green in color, were removed. The liver could then be plainly felt and was decidedly hard.

30*th.* Some pain at the right base and a pleural friction sound. Blood: Red blood corpuscles, 5,300,000; white blood corpuscles, 7200; hemoglobin, 80 per cent.

December 1*st.* Considerable reaccumulation of abdominal effusion. Right-sided hydrothorax.

5*th.* Increase in effusion in right chest; white blood corpuscles, 7400. Urine: specific gravity, 1030; small amount of albumin, leukocytes, a few red blood corpuscles, urates, a few hyaline casts. There is a trace of bile.

16*th.* Abdomen tapped; twelve pints fourteen ounces removed.

January 3, 1904. Abdomen tapped; sixteen pints fifteen ounces removed. The fluid does not contain bile.

14*th.* Abdomen tapped; eighteen pints eight ounces removed. Right pleural cavity tapped; fourteen ounces of blood-tinged fluid removed. Soon after this the patient passed out of observation.

The most interesting feature in this case was the fact that she had been under my observation a year previous to her admission to the hospital, at which time I found great enlargement of the spleen without a single symptom of consequence. It was not until long after that time that she first showed evidences of beginning cirrhosis and portal obstruction. There was not in the history of this case any hemorrhage nor the usual gastrointestinal symptoms met with in splenic anemia.

CLASSIFICATION OF SPLENIC ANEMIA. Analysis of the clinical descriptions and pathologic features of many of the cases classified as splenic anemia discloses the fact that these cases properly belonged to one or the other of the following conditions :

1. *Progressive Pernicious Anemia or Intense Secondary Anemia.* The oft-cited case of Strümpell belongs to this group. In that case, probably one of pernicious anemia, simple congestion with great dilatation of the splenic sinuses constituted the pathologic condition of the spleen. Other cases in which pronounced anemia and moderate enlargement of the spleen have been found should be included in this group, and these constitute the basis for the view now seldom expressed, that splenic anemia and progressive pernicious anemia are closely allied. As a matter of fact, in the conditions nowadays classified as splenic anemia impoverishment of the blood is rarely a predominating feature except after repeated hemorrhages.

2. *Pseudoleukemia.* The earliest writers (Griesinger, H. C. Wood) suggested that the condition is usually a splenic variety of Hodgkin's disease, and this view is occasionally expressed at the present day. This opinion was adopted by Sippy in his admirable review of the subject, but is now generally abandoned for the reason that the pathologic anatomy as far as known almost invariably negatives the supposed pseudoleukemic nature of the disease. Nevertheless there are some cases reported in older (Müller) and more recent literature in which the symptoms and such pathologic data as were obtained show that splenic pseudoleukemia may be, clinically, nearly if not quite identical with that we now call splenic anemia. Such cases are, however, exceptional.

3. *Leukemia.* All systematic writers call attention to the occasional subsidence of leukocytosis in this disease. Under these circumstances the case might for a time have many of the clinical features of splenic anemia, and some authorities (Griesinger) regarded the latter as an aleukemic variety of splenic leukemia.

4. *Cirrhosis of the Liver.* Some degree of splenic enlargement is habitual in cirrhosis of the liver. Formerly this was attributed to congestion of the spleen caused by obstruction of the portal circulation, but more recently the view has gained ground that the splenic condition results from the action of the same irritant as that which causes the cirrhosis (alcohol, etc.). Under these circumstances it might seem natural that certain cases of cirrhosis should present an unusual degree of splenic enlargement. The

studies of Banti, showing a frequent association of splenic anemia and cirrhosis, gave additional color to this view and seemed to justify the expression *splenomegalic cirrhosis of the liver*. On the other hand, however, the investigations of Banti, Bovaird and others showed that clinically as well as pathologically the cirrhotic process may be demonstrably secondary to the splenic disease. Under such circumstances the condition is rather one of *splenomegaly with cirrhosis*. The cases in which pronounced splenomegaly is simply an incident in cirrhosis are probably rare as far as accurate studies would indicate.

5. *Hypertrophic Cirrhosis of the Liver* (Hanot's disease). In this condition the long duration of the disease and the considerable degree of splenic enlargement are the bases upon which inclusion under the head of splenic anemia has sometimes been suggested, if not justified. Some of the cases of familiar splenic anemia in particular may perhaps be more properly classified here.

6. *Chronic Splenitis*. The greatest confusion exists in the case of splenic enlargement in children. Such enlargement is common in rickets and congenital syphilis, and occurs in the uncertainly classified condition called anemia infantum pseudoleukemica (von Jaksch). In the case of rickets and congenital syphilis the splenic lesion is a chronic splenitis leading to fibroid change and some lymphadenoid hypertrophy. Clinically, the dominating symptoms are those of the underlying affection. It is, of course, possible that exceptionally the splenic enlargement and its consequences might overshadow other features, but the evidence at hand does not bear out such an assumption. In the case of von Jaksch's disease, pathologic studies and accurate clinical observations also are still wanting.

The chronic splenitis of malaria belongs in the same group. How far malaria may prove to be a factor in the etiology of splenic anemia remains unsettled. Undoubtedly, however, there is some added element that operates in the development of the condition even if malaria is a factor.

Leaving out of consideration the cases of splenic enlargement, which by their clinical features or pathologic lesions could plainly be referred to the above groups, there remain certain cases in which

the splenic disease is of such dominating character that the cases must be regarded as forming a separate group or separate groups. The fact that cirrhosis of the liver supervenes in the late stages does not militate against such a classification, since very good evidence has been brought forward to show that splenic disease may occasion secondary cirrhosis of the liver. Conspicuous predominance of splenic involvement from the beginning warrants the separate classification of such cases, even when some evidence of cirrhosis of the liver is an early feature.

It would be hopeless in the present state of knowledge to attempt a classification of all of the cases that have been reported. On the other hand, it is very evident that there are very different sorts of cases that have more or less superficial resemblance, and I cannot share the view that all are probably instances of one disease in different stages. The ultimate solution of the matter must, seemingly, come from more careful clinical and pathologic study of these cases, with recognition of the fact that the long continuance of the disease may cause very different lesions at different stages. The following varieties may be recognized provisionally :

1. *Simple Splenomegaly.* In a certain number of cases, including some described by Müller, Banti, Osler, Rendu, Peter, Sippy and others, the conspicuous feature in the clinical history is the splenic enlargement. Anemia is not by any means an invariable symptom, though usually present, especially when hemorrhages occur. The hemorrhages may be a purely splenic feature in the sense that they are caused by mechanical obstructions brought about by traction on the splenic vein, or they may be caused by general conditions less readily explained, as, for example, in the case of hemorrhages from the gums. Pathologically speaking, this variety belongs in the category of chronic splenitis such as occurs secondary to malaria, syphilis, rickets and chronic gastrointestinal diseases. The lesion is essentially a fibrous hyperplasia. In some instances the endothelial cells of the sinuses are swollen, and large macrophages are found ; in others these cells are not observed, possibly on account of the late stage at which the disease has terminated. Analogy suggests that some form of chronic infection or intoxication is the cause of this variety. The tendency to some endothelial

proliferation does not exclude this view, for in all kinds of chronic splenitis such endothelial processes may occur. In some cases the disease may persist for a long time, and the patient may ultimately die without additional lesions; in other cases changes in the liver develop as a final stage and cause a marked alteration in the clinical features. These latter cases are, I believe, in some sort different from the former in their pathology, and may for convenience be separately classed as

2. *Simple Splenomegaly Terminating in Cirrhosis of the Liver.* Perhaps the cases which ultimately develop cirrhosis of the liver and assume the fully developed character of Banti's disease are cases which from the start had a prominent grade of endothelial proliferation in the splenic sinuses. Banti has shown that there may be an endophlebitis extending from the spleen to the splenic vein, and eventually to the portal vein, and he referred the cirrhosis of the liver to this cause. In the cases recently reported by Dock and Warthin, stenosis of the portal vein was discovered, and this may have been preceded by a similar endothelial process. In one of my own cases there were, within the terminals of the portal vein in the liver, large endothelial cells corresponding to those found in the splenic sinuses and in the regional lymphatic glands. In Bovaird's case large endothelial cells corresponding with those found in the sinuses of the spleen were a conspicuous feature in the portal spaces of the liver. The probable embolical origin of these formations could not be overlooked. All of these facts suggest that cirrhosis of the liver as a termination of splenomegaly is particularly likely to occur when the process from the beginning has been inclined to affect the endothelial cells in the splenic sinuses particularly. A review of the cases reported in the literature discloses the varying degree of endothelial proliferation that may be present, and it seems likely to me that this is not the result merely of the different stages at which the examinations happened to be made, but rather the consequence of natural difference in the pathology of different cases. Even accepting this, however, the difference may be only one of degree.

That splenomegaly may actually precede cirrhosis of the liver, or at least any considerable degree of cirrhosis, was shown dis-

tinctly by one of my cases (Case V.), here reported, in which the patient had been under my observation for over a year preceding the final development of the well-known symptoms of Banti's disease. When she came under observation there was a decided enlargement of the spleen, but no other signs of illness.

3. *Splenomegaly with Marked Constitutional Disturbances.* A certain number of cases of splenomegaly have been described in which, in addition to the enlargement of the spleen, there has been a profound disturbance of the general health, causing a stunted growth, clubbed fingers, osseous changes and pigmentation of the skin. Gilbert and Fournier report a group of such cases in children in whom the symptoms were those enumerated, together with enlargement of the liver and jaundice. Frederick Taylor has also reported a series, and refers to the case of H. R. Smith, another presented in the Medical Society of the Hospitals of Paris and some other less certain instances. In some particulars the group of family splenomegaly described by Brill is analogous, though in other particulars more suggestive of the variety of simple splenomegaly. In considering these cases, which have for the most part been observed in young persons or children, the difficulty of distinguishing the disease from hypertrophic cirrhosis of the liver (Hanot's disease) must be kept in mind. Furthermore, pigmentation of the skin of non-icteric character may be accounted for in various ways, and in some of the reported instances the possibility of its being arsenical must be remembered, while in other cases the whole condition may belong to that uncertainly defined affection called hemochromatosis, in which cirrhosis of the liver is often an incident. Leaving out uncertain cases, however, there seems to be a group or variety in which splenomegaly is associated with stunted growth, pigmentation of the skin, clubbing of the fingers, and other evidences of general systemic disturbances.

In this group probably belong two of the cases here reported. These presented very different clinical features from those shown by other instances of so-called splenic anemia or splenomegaly.

4. *Splenomegaly Primitive.* While it is not possible perhaps to distinguish this variety clinically, there is a sharp distinction in the pathologic features. It will be recalled that the essential

characteristic of this condition is the presence of irregular oval spaces surrounded with fibrous tissue, and more or less filled with large endothelial cells containing one or more nuclei. All writers agree that these alveoli are formed by the proliferation of the endothelial lining of the splenic sinuses, with fibrous hyperplasia of the surrounding tissue, causing the formation of a coarse reticulum.

Bovaird has suggested that the proliferated endothelial cells eventually form fibrous tissue, and Rolleston and Osler are disposed to admit this as a probability. Harris and Herzog dissent from this opinion. When the descriptions and figures of the cases of Gaucher, Picou and Ramond, Collier and Bovaird are examined it may not seem impossible that the endothelial process might be the forerunner of an ordinary fibrous change ; that, in other words, as Rolleston states, the endothelial proliferation may be replaced by a fibrous-tissue process. When, however, the macroscopic as well as the histologic features in my own case are considered, it will be seen that the transformation into the ordinary characters of a fibrous splenitis could not have occurred after a lapse of any amount of time. From every point of view the case suggests a neoplasm. In reporting his case Bovaird considered the respective merits of the neoplasm and hyperplasia theories, and concluded that the condition was rather one of endothelial hyperplasia. He referred to the doctrine of Thoma, that a tumor must be an autonomous growth. On the other hand, all pathologists are agreed that there is no sharp dividing line between the processes which may be properly called hyperplastic and those which are, strictly speaking, neoplastic. In reviewing the cases of splenic anemia in which the endothelial hyperplasia has been a feature it will be seen that there are all grades of conspicuousness of this part of the pathologic processes—from those cases in which the predominating feature is a fibrous hyperplasia, with a certain element of endothelial proliferation superadded, up to those cases like my own (Case III.), in which the macroscopic features of the condition were those of a tumor and the microscopic characters those of an active neoplastic formation, essentially and primarily involving the endothelial cells.

PATHOLOGIC ANATOMY. Compared with the mass of clinical material the pathologic data are scant and unsatisfactory. In part this is due to the chronicity of the disease, and in part to the fact that the examinations have been made at various stages, when presumably diverse conditions might be expected. The most extensive of the more recent studies are those of Banti. In brief the following notes contain the results of his examinations:

The spleen is much increased, weighing from 1 to 1.5 kilograms. The shape is preserved, the surface smooth and regular. The capsule is thickened, and on section the substance is dark brown and hard, showing thickened trabecula and whitish nodules which correspond to the Malpighian bodies.

Microscopically the Malpighian bodies were found in various stages of fibrous transformation, the process beginning around the vessel within the body. A certain amount of hyaline transformation was also apparent. The splenic pulp showed no special enlargement of the venous channels. In the earliest stage there may be found in some of the veins a lining of large cells, making the vessel appear almost like an epithelial channel on cross-section. These large cells have a limited amount of protoplasm and a large nucleus of a diameter of from 5 μ to 8 μ. The same kind of cells are found in the reticulum surrounding the veins, and in some of the channels the cells have become loosened from the walls and fill the lumen of the vessel, giving the appearance of a cancerous alveolus. In some spaces actual giant cells and occasionally cells containing normal or degenerated red corpuscles were observed. The reticulum of the pulp was evidently thickened and of hyaline appearance. This was always a conspicuous feature, and distinguished the tissue absolutely from normal spleen. The thickening of the reticulum is in proportion to the duration of the disease, and finally areas of the splenic pulp may become entirely fibrous. In view of the process of fibrous transformation and the multiplication of cells within the veins, Banti proposed the name "fibroadenia." He does not believe there is a new-formation of fibrous tissue in the ordinary sense of the term, but rather an increase of the reticulum from exudation from pre-existing cells.

The liver is reduced in size, granular and hard. In earlier stages of the disease it may be normal in size and smooth. Microscopically there is found a marked interlobular cirrhosis like that due to alcohol.

Banti calls particular attention to sclerotic endophlebitis of the splenic vein, causing irregular thickening and sometimes even atheromatous and calcareous foci. These conditions also extend into the portal vein, and in the ascitic stage of the disease even the mesenteric veins may be affected, though in less degree than the splenic.

The bone-marrow showed all the characteristics of fetal marrow, but nucleated red corpuscles were present in small numbers.

Bacteriologic examination of various tissues and the blood proved negative.

Most of the reports published since Banti's correspond in all essential details.

According to Osler,[1] two conditions have been described in the spleen: (1) a fibrosis and hyperplasia with atrophy of the pulp and a hyaline degeneration of the Malpighian bodies, and with this description, according to MacCallum, Osler's cases Nos. 4, 5 and 16 correspond; (2) on the other hand, very remarkable change is found in certain cases which agree in every clinical particular with the definition of the disease as given for ordinary cases. The normal texture of the spleen is replaced by fibrous tissue and large endothelial cells with clear protoplasm containing two or more nuclei, and among them giant cells. This was the condition first described by Gaucher as primary endothelioma.

Sippy[2] could find records of but ten postmortems in which he felt reasonably certain that the cause of death was "splenic pseudoleukemia." The liver was usually enlarged, the surface smooth, the edges rounded and no evidence of cirrhosis, though under the microscope slight increase of the interlobular connective tissue may be found. The spleen is always increased in size, and there may be perisplenitis. Its surface is usually smooth, but sometimes peritoneal adhesions have been recorded. In a case reported

[1] Transactions of the Association of American Physicians, 1902, p. 429.
[2] American Journal of the Medical Sciences, November, 1899.

by Banti there was visible increase in the connective tissue, and small white areas about the size of a pea were noted, and these proved to be made up of connective tissue. In Sippy's case there was no macroscopic evidence of connective tissue, but microscopically considerable fibrosis was the feature of interest. Banti summarizes the findings in the spleen as follows: (1) atrophy and sclerosis of the Malpighian corpuscles, and (2) substitution of a fibrous reticulum for the delicate reticulum of the splenic pulp. As a rule, according to Sippy, the Malpighian bodies have been found but slightly altered. In his own case a few were sclerosed, the greater number showing no change. The following is quoted from the description of West ("A Case of Splenic Anemia, Splenomegalie Primitive," *Medico-Chirurgical Transactions*, 1896): "The spleen showed slight increase in the trabecular tissue—*i. e.*, slight fibrosis. Malpighian corpuscles are much diminished in size and badly developed. Iron reaction negative." Kanthack examined the tissues in West's case and referred to the presence of giant cells in addition to the fibrosis.

Sippy does not quote extensively from others regarding the pathologic anatomy, leaving the impression that the histology as observed by others was practically the same as given in the above.

Dock and Warthin[1] report two cases with anatomical studies. In the first the liver was small and showed a moderate increase in connective tissue, especially in one area. The spleen had a thickened capsule and showed a dense fibrous network enclosing enlarged blood spaces. These were lined, and in many cases partly filled with large endothelial or reticular cells containing one or more lightly staining nuclei, and in the majority of cases nucleoli. "The fibrous tissue represents a hyperplasia of the reticulum of the pulp, the endothelial cells lining the blood spaces apparently taking part in the formation of the new fibrous tissue."

The bone-marrow was red and contained an increased number of normoblasts and very few giant cells. The retroperitoneal glands were enlarged and of the type known as hemal gland.

In their second cases the liver was small, adherent to the

[1] Transactions of the Association of American Physicians, 1903.

diaphragm by tough adhesions, and the surface on section was granular. It was the picture of an atrophic cirrhosis on microscopic examination.

The spleen showed marked fibrosis with hyaline change of the new-formed connective tissue. This process was uniform throughout the organ. The blood spaces were lined by large hypertrophic endothelial cells. A few giant cells were found in the blood spaces, and the author suggests that these may have been embolic and of bone-marrow origin.

In both of the cases there was a stenosis of the portal vein, and as the pathologic lesions are entirely compatible with chronic congestion of the spleen they suggest that the condition of the portal vein may have been the cause of the lesion.

They find nothing in recent accounts of splenic anemia suggesting the occurrence of this condition of the portal vein, but several cases were reported by Sir Andrew Clark.[1] The lesions of the splenic and portal vein described by Banti differed somewhat from that reported by Dock and Warthin, though perhaps later stages of the conditions observed by Banti might correspond.

Williamson[2] describes a case which came to autopsy and in which the histologic features were sclerosis of the Malpighian bodies, general fibrous hyperplasia, great congestion of the pulp, and sinuses filled with large corpuscles containing cells. The last-named cells contained from six to ten red corpuscles, and were mononuclear. I find no other recorded case with such conspicuous macrophages. Allusion is made by some authors to occasional large endothelial cells containing red corpuscles or fragments of such, but not to the numbers found by Williamson, nor to cells of the peculiar character figured by him. In a case studied by Rolleston, the spleen, weighing thirty-seven ounces, "showed fibrosis with widespread proliferation of the endothelial cells and disappearance of the leukocytic elements."

Taylor, in referring to one of his cases of "splenomegalic cirrhosis of the liver," states that "the spleen was loaded with red corpuscles; otherwise it appeared normal."

[1] Transactions of the London Pathological Society, 1867.
[2] Medical Chronicle, May, 1893.

One cannot read the accounts of pathologic examinations, scanty and unsatisfactory as they are, without receiving the impression that they very probably refer to different pathologic conditions, however similar the clinical features. There are three sorts of changes that may be clearly distinguished: (1) congestion, (2) fibrous transformation, and (3) endothelial proliferation. The first of these was conspicuous in only a few of the cases, and is more prominent in instances (like that of Strümpell) of doubtful character. Fibrous hyperplasia of the splenic reticulum and sclerosis of the Malpighian bodies constitute a marked condition in nearly all of the cases—a fact which is, of course, easily explained by the chronicity of the disease and the late stage at which the histology has usually been studied. What the conditions might have been at earlier stages cannot be determined by such examinations. The endothelial proliferation is not peculiar to cases of so-called splenic anemia. A certain amount of such proliferation is found in cases of infectious splenitis of all kinds, and this doubtless contributes, in such cases as in splenic anemia (Bovaird, Rolleston, Osler, Dock and Warthin), to the fibrous change in the reticulum.

A very different condition is that first described by Weichselbaum as "Primary Multiple Endothelial Sarcoma of the Spleen," and later by Gaucher as "Epithelioma primitif," and by Debove and Bruhl as "Splenomegalie primitive." Among the cases of this description are those of Weichselbaum, Gaucher, Collier, Picou and Raymond, Bovaird and my own (Case III. of this series). The case of Weichselbaum and mine differ from the others in having a more marked neoplastic appearance on macroscopic examination. The opinion of Birch-Hirschfeld that Weichselbaum's case was one of endothelial hyperplasia rather than a tumor does not accord entirely with the gross appearance of the organ, though it is more applicable to Weichselbaum's case than to my own. This will appear from the recorded description.

Weichselbaum[1] remarks, by way of preface, that he was unable to find any instance of primary sarcoma of the spleen in the litera-

[1] Virchow's Archiv, 1881, vol. lxxxv. p. 563.

ture. The specimen was obtained from the body of a soldier aged twenty-one years. No clinical data are given. The spleen was "somewhat enlarged," hard, dark brown in color and presented visible follicles. On section the surface was found studded with small nodules the size of a millet-seed or pea, grayish-red in color, rather soft and projecting above the cut surface. Their color distinguished them sharply from the splenic tissue, but there was no other sharp demarcation. On microscopic examination there was found a fibrous reticulum, coarser than that of the normal reticulum of the spleen, but no distinct alveolar arrangement. In the meshes of the reticulum were found large endothelial cells of round, oval or irregular shape, some of the latter having projecting processes. The nuclei were large and often double. In the periphery of the masses large cells containing remnants of red corpuscles or yellowish pigment were found. In the same region extension of the processes of the cells into the fibrous reticulum was observed. All other organs were uninvolved.

In Collier's case the involvement of the spleen was in the form of a zone of cortical infiltration, and Bovaird describes pyramidal formations of white or yellowish-white color extending deeply into the substance of the organ, and involving the greater part of its anterior half, while the posterior half was comparatively free. In Picou and Raymond's case the macroscopic appearance of the organ is not described with sufficient accuracy. In none of these cases was the condition so similar to that of definite neoplasms as in mine. It is not impossible, though difficult, to conceive how in any of these cases a longer duration could have led to an effacement of the conspicuous cellular process and a conversion by fibrous hyperplasia into an organ such as those previously described in cases of ordinary splenic anemia. It may be admitted as probable that endothelial proliferation is a precursor of some of the fibrous-tissue formation in splenic anemia as well as in chronic splenitis, just as the same process may lead to sclerosis in the peritoneum; but it seems to me just as unlikely that the endothelial process in the six cases under consideration could have terminated in complete fibrosis as that endotheliomata of the peritoneum may have a like conclusion.

It is always difficult to draw sharp lines between cellular hyperplasias and tumors. In the case of glandular affections of the gastrointestinal mucosa, in certain epithelial proliferations in the liver, thyroid gland and breast, this difficulty is well recognized. The microscopic features alone do not suffice, and an appeal must be made to the gross appearances, the etiologic relations, etc. Viewed in this way, I cannot avoid the conclusion that my own case belongs in the category of tumors rather than of simple cellular hyperplasia. The peculiar prominence of giant cells naturally raised the suspicion that the process might be infectious or parasitic, but no form of bacterial organisms nor anything suggesting protozoa could be discovered.

One of the arguments advanced in opposition to the tumor theory in such cases is the preservation of normal splenic appearances. As one author states, "After all these years the organ is still a spleen." This preservation of normal appearance is, however, more superficial than real, as sections through the organ showed in several cases almost complete transformation of the splenic substance.

The conclusion to which I have come is that the cases of splenomegaly of the type of Gaucher represent a primary neoplasm of the spleen somewhat comparable to the diffuse myelomata, and to certain infiltrating sarcomata of the liver.

DISCUSSION.

Dr. Osler: I think these interesting cases illustrate the extreme complexity of the subject and the very diverse conditions that have been grouped together under the same unfortunate name of splenic anemia. I think there can be no doubt that such a case as the third one is pathologically and etiologically one to which, with a number of cases, we have given this caption. It belongs to a definite group, but the point of interest is they can hardly be recognized clinically.

Could the average clinician make the differentiation he would more frequently send such cases to the surgeon, for they belong to a group in which operation offers the best hope.

Since my last report here I have had nine cases of great enlargement of the spleen with anemia. They may be grouped into four sections. Cases that may be called primitive splenomegaly; one patient had an enormous spleen for years with no symptoms except the discomfort of the enlarged organ. She had no particular anemia, and her blood count was above normal; just a slight lowering of the hemoglobin.

There were four cases of chronic splenic enlargement with a moderate grade of pigmentation of the skin and, in some, recurring hemorrhages.

Two cases belonged to a group that needs more careful study than has been given to them both with regard to their relation to Hanot's disease and to the hereditary form described by Brill, of New York.

Fourthly, I had one case of enlarged spleen with an acute anemia of the progressive pernicious type. The subject is a complicated one, but we are working in the right direction, and such papers as Dr. Stengel help to clear the field.

DR. DOCK: I would like to add a word in regard to the importance of further anatomic study of this subject. In working over the literature of endothelioma of the spleen a year ago I got the impression that under that name a variety of conditions was described. Dr. Stengel's third case is unique in many respects, and the macroscopic and microscopic alterations strongly suggest infection. Although proliferation of endothelial cells occurs in many cases of splenic anemia in the narrower sense, yet these proliferations do not suggest tumor formation. In the splenic vein in the case reported by Dr. Warthin and myself last year the proliferation was not extensive, but sclerosis was marked. I wish to speak in favor of more frequent attempts at extirpation in cases of splenomegaly of obscure origin, but without evidences of bone-marrow disease or other serious contraindications. Such operations would not only do good in many cases, but they would be certain to add much to our knowledge of the symptomatology and pathology of spleen disease. I would like to hear Dr. Sippy in regard to this subject, on which he has done such important work.

DR. SIPPY: I shall not mention but one of the cases I have seen since the report I made in 1889. It was a woman with a movable spleen that came down below the umbilicus and readily moved about in the abdominal cavity. She presented the picture of a gradually developing anemia. The red blood cell count showed 3,000,000, no nucleated reds, and hemoglobin of 40 per cent. From the clinical picture and the fact that the spleen was very much enlarged, I advised operation. The spleen was removed, and she was under observation over a month. During that time her blood picture changed. When she left the hospital the hemoglobin was 68 per cent., the red cells had increased to 4,000,000. From her attending physician I hear that she is still doing well. At the same time she had some digestive trouble. She was undernourished and not eating enough. The question arises, Was her splenic anemia due to

poisonous substances secreted by this enlarged spleen or was it an anemia from malnutrition? Examination of the spleen showed the ordinary splenic hyperplasia. There was no evidence of sclerosis of the liver and no enlargement of the glands. I think the distinctive type of this disease is one that has a progressive course. My longest case published was three and a half years, but Dr. Osler has reported some in his list of longer standing.

DR. CABOT: There is one point that Dr. Sippy has brought out that I should like to refer to. I think there is no evidence, clinically or experimentally, that splenic anemia is ever due to malnutrition. That may certainly be excluded.

DR. OSLER: May I add a word in regard to the importance of looking in the blood in these cases for the protozoon of Donovan, especially in the cases coming in now from the tropics.

DR. WELCH: Dr. Carroll has some very beautiful specimens of this organism. Perhaps he will show them to the members at this session.

DR. CARROLL: I am sorry, but those specimens are in Dr. Welch's laboratory.

DR. STENGEL: I want to say that the young woman from whom this spleen was taken was a person apparently in excellent health, and there was no suspicion of malnutrition in her case. Repeated examination of this tissue for the tubercle bacilli failed to show any.

With respect to distinguishing these cases clinically, the day this patient came to me I had three cases of splenic anemia, and they were all distinctive in character. Some light is beginning to break in on the differentiation of types of this disease; the stunted growth type is certainly characteristic.

THE INFLUENCE OF SUPRARENAL EXTRACT UPON ABSORPTION AND TRANSUDATION.

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In a series of experiments on frogs adrenalin seemed to have a distinctly delaying influence upon the toxic effect of strychnin. The following abbreviated protocols of some experiments will illustrate it:

Experiment 1. Frog I. received an injection into the dorsal lymph sac of 0.03 mg. of strychnin nitrate + 0.7 c.c. pure adrenalin (mixed in the syringe). Frog II. received 0.03 mg. strychnin nitrate + 0.7 c.c. normal salt solution (also mixed in the syringe). Frog II. had the first tetanus twenty minutes after the injection, while in Frog I. the first tetanus appeared seventy minutes after the injection.

In this experiment the tetanus in the animal which received adrenalin with the strychnin was delayed fifty minutes. In experiments in which larger doses of strychnin were employed the delaying effect was less pronounced.

Experiment 2. Frogs I. and II. received into the ventral lymph sacs first 0.6 c.c. adrenalin, and a little later 0.04 mg. strychnin nitrate. Frogs III. (control I.) and IV. (control II.) also received into the ventral sac 0.04 mg. strychnin. Frog III. (control I.) had a tetanus after twenty minutes, and Frog IV. (control II., a much larger frog than the rest) after fifty-five minutes. Frogs I.

and II. had the first tetanic outbreaks seventy-five minutes after injection, and the tetani were weaker and of shorter duration than in the control animals.

In both kinds of experiments the adrenalin came in direct contact with the strychnin, either within the syringe or in the lymph sacs of the animal. By both these methods the toxic effect of strychnin was unmistakably mitigated. How ?

The mitigating influence of the adrenalin could be thought to be due to some chemical action upon the strychnin, especially since in these experiments both substances came into more or less intimate contact. On the supposition that in a biochemical interaction the effect ought to be greater the longer and the more intimately the substances are mixed, in a second series of experiments the adrenalin and strychnin were well mixed and kept for many hours before injection into the frogs, evaporation being guarded against. It was expected that if the delaying effect were due to some biochemical interaction, the mitigation of the toxic effect of strychnin would improve with the length of time the substances were mixed before injection. The experiments, however, did not bring out such results ; on the contrary, in some experiments the delaying effect of the addition of adrenalin seemed to have been entirely lost when the mixture stood a long time before it was injected. However, while the results could not be utilized in support of this hypothesis, they do not disprove that the delaying effect of the adrenalin might be due to some biochemical interaction.

Another explanation might be found in the assumption that the mitigating action of adrenalin could be due to its paralyzing effect upon the central nervous system. In order to obtain our results with the strychnin experiments we had to use no less a dose than 0.5 c.c. of adrenalin. Such a dose, however, has a pronounced prostrating effect upon medium-sized frogs. The animal does not sit up, but lies flat on the table, the head touching it, and is hardly able to fight when it is lifted by one leg. According to Oliver and Schaefer,[1] this is due to a depression of the central nervous system. We could then assume that this paralyzing effect of adre-

[1] Journal of Physiology, 1895, vol. xviii. p. 230.

nalin upon the nervous system neutralizes somewhat the effects of strychnin upon it; hence the delay in the appearance of the tetanus. This hypothesis, however, was disproved by a series of experiments in which the adrenalin was injected in one lymph sac (dorsal or ventral) and the strychnin in the other lymph sac of the animal. While there was an unmistakable prostration of the animal, no apparent delay in the toxic effect of the strychnin could be observed by this method of injection, as will be seen in the following illustration:

Experiment 3. Three frogs (controls) received into the dorsal lymph sacs 0.04 mg. strychnin each. Three other frogs received each into the dorsal lymph sacs 0.5 c.c. adrenalin, and after ten minutes 0.04 mg. strychnin was injected into the ventral lymph sacs. In none of the adrenalin animals did the toxic effect appear later than in the control frogs.

In this group of experiments the adrenalin certainly caused no mitigation of the effect of strychnin. However, the objection could be raised here that the controls received the strychnin into the dorsal lymph sac, while in the adrenalin animals the strychnin was injected into the ventral sacs. And since the adrenalin animals were lying flat on their bellies, the pressure hereby exerted upon the contents of the ventral lymph sac might facilitate absorption, and thus overcompensate the retardation caused by the administration of adrenalin. Such objections, however, cannot be raised against the following experiments:

Experiment 4. Frog I. received 1.2 c.c. adrenalin into ventral sac and 0.05 mg. strychnin into dorsal sac. Tetanus after twenty minutes. Frog II. (control) received into dorsal sac 0.05 mg. strychnin. Tetanus in thirty minutes.

In this and other similar experiments in which the strychnin was injected into the dorsal and the adrenalin into the ventral lymph sacs the animals were deeply prostrated from the large dose of adrenalin. Nevertheless, in none of these cases was there a marked delay in the toxic effect of the strychnin. We may therefore conclude that the delay which was observed in the experiments in which there was intimate contact between the two substances could not be due to a neutralizing effect upon the central nervous system.

Our experiments on frogs brought out then these two facts:

When adrenalin and strychnin are mixed before injection, or when both substances are injected into the same lymph sac, the well-known toxic effect of strychnin is distinctly delayed and mitigated, while no such mitigation could be observed when the two substances were injected into different parts of the animal where they could not come into immediate contact.

As an explanation of these facts, the theory of a biochemical interaction between these substances could so far neither be sustained nor disproved. But there is still another quite plausible theory. We know that a local application of suprarenal extract to any tissue of the animal body causes a constriction of its blood-vessels—a blanching of that tissue. We might assume that the absorbing power of the tissues when in such a state is impaired. Now when adrenalin and strychnin are mixed together, either within the syringe before injection or within the same lymph sac, the tissue which is to absorb the strychnin is subjected to the influence of adrenalin, and its power of absorption might become impaired; hence the delay in the toxic effect of the strychnin. In other words, the mitigating effect of adrenalin consists in the impairment of the absorbing power of the tissues with which it comes in direct contact. An introduction of adrenalin into the animal by subcutaneous injection brings only little to each of the tissues of the body, and might thus be insufficient to impair their absorbing power; hence the failure to delay the effect of strychnin when the adrenalin is injected into another place than the strychnin. The essence of this last hypothesis, the effect of suprarenal extract upon absorption, has been studied extensively by us in several series of experiments, especially on rabbits, and on the basis of an assumption which we will state later. However, while our investigation was already quite far advanced, we discovered that the same subject was treated in two very recent publications by Alfred Exner. We shall, therefore, before continuing the report upon our own experiments, discuss the findings of this author and the interpretations he gives to them.

In the first series of experiments Exner[1] injected adrenalin into

[1] Zeitschrift f. Heilkunde, 1903, Abteilung Chirurgie, p. 302.

the peritoneal cavity of rabbits and guinea-pigs, and subsequently injected strychnin nitrate into the same place. In nearly all the cases there was more or less retardation of the toxic effects of strychnin. Similar results were obtained in experiments with potassium cyanid and physostigmin. In other series of experiments substances were introduced into the peritoneal cavity which appear in the urine, where they are easily recognizable. Urine was obtained by expression of the bladder. It was found that the previous intraperitoneal injection of adrenalin retarded somewhat the appearance of sodium indigosulphate and sodium salicylate in the urine, but had no perceptible effect upon the appearance of potassium iodid. Furthermore, after an intraperitoneal injection of an emulsion of paraffin and mucilage the presence of a small quantity of paraffin in the blood could be demonstrated, and Exner states that after a preceding intraperitoneal injection of adrenalin the quantity of paraffin present in the blood was much less. Since the emulsion of paraffin could be absorbed only through the lymphatics, Exner comes to the conclusion that adrenalin impairs the absorption by the lymphatics, but not that by the bloodvessels; hence the difference in the effect upon different substances. Potassium iodid is absorbed through the bloodvessels, its absorption is therefore not impaired by a previous injection of adrenalin. On the other hand, strychnin, potassium cyanid, physostigmin, sodium indigosulphate and sodium salicylate, Exner assumes, are essentially absorbed through the lymphatics. Finally, in a few incomplete and unconvincing experiments, Exner found that the absorption of toxins (abrin) is not influenced by a previous intraperitoneal injection of adrenalin, but that such an injection retards the absorption of bacteria (proteus vulgaris) into the blood.

In a second communication Exner[1] found that with a single exception intraperitoneal injections of adrenalin did not retard the toxic effect of strychnin when the latter was injected subcutaneously. The intraperitoneal injection of adrenalin had, however, a distinctly retarding influence upon the effects of strychnin and

[1] Arch. f. exper. Pathol. u. Pharmakologie, 1903, Bd. l. p. 313.

physostigmin when these substances were introduced into the stomach of the animal.

In the experiments of Exner, with the exception of potassium iodid, the absorption of all substances from the peritoneal cavity was retarded by a previous intraperitoneal injection of adrenalin. Such an injection, however, did not affect the absorption of strychnin when administered subcutaneously. So far these observations coincide with our experience with frogs, namely, that a retardation occurs when both substances come in contact, but not when they are injected in separate localities. But Exner's experience with the absorption from the stomach would seem to demonstrate that the (non-intravenous) application of adrenalin in one place is capable also of retarding the absorption from another place. An analysis of Exner's observations will show, however, that they permit an entirely different interpretation than the one given to them by Exner. The fact that the intoxication with strychnin, for instance, appeared so much later in the adrenalized animals was taken by Exner to show that the absorption from the stomach was retarded. In a series of experiments published some years ago by one of us it was clearly demonstrated that strychnin is not absorbed within the rabbit's stomach,[1] and is very little absorbed in the stomach of the dog.[2] This has since been repeatedly confirmed. The toxic effect of strychnin when introduced into the stomach is due to its transportation into the intestines, where it is rapidly absorbed. When the movements of the stomach are impaired, for instance, after cutting the vagi, the toxic effect is considerably delayed, due to a retardation in the removal of the strychnin from the stomach into the intestines. It takes some time until the strychnin has accumulated within the intestines to an effective minimum dose, especially since some fractions of it are meanwhile eliminated again. Now, according to Langley,[3] the extract of suprarenal bodies causes inhibition of the movements of the stomach. Therefore we may justly assume that the retardation of the toxic effect of the strychnin introduced into the stomach, which Exner observed, was not

[1] Journal of Experimental Medicine, 1895.
[2] American Journal of the Medical Sciences, November, 1899.
[3] Journal of Physiology, 1901-1902, vol. xxvii. p. 237.

due to an impairment of the absorbing power of the stomach, but to an inhibition of the movements of this organ. The theory of Exner, that adrenalin affects the absorption by the lymphatics and not that by the bloodvessels, we shall discuss later.

In our experiments on frogs, and practically also in the experiments of Exner, the delaying effect of adrenalin was observed only when the toxic or other substances were applied to the same tissues to which previously adrenalin was applied. When the two substances were incorporated in different parts of the body the delaying effect of adrenalin was not demonstrable. (Exner's observations on the intragastric application of strychnin, etc., are no exception, since they permit, as stated above, another interpretation.) This fact is very well compatible with the theory that the delaying effect of adrenalin is due to an impairment of the powers of absorption of the tissues. The tissues to which the adrenalin is directly applied receive a dose of this substance sufficient to affect them profoundly in some way so as to render them unable to absorb, to carry into the circulation any substance with which they subsequently come into contact. Other tissues of the animal body, however, will be affected by the application of adrenalin to a distant part only by so much as would be absorbed into the blood and carried to them. The amount of adrenalin which these tissues will thus receive will be very minute, and could exert hardly a perceptible effect. We should also bear in mind that if the direct contact with adrenalin impairs the absorption, the adrenalin itself, when injected intraperitoneally or subcutaneously, would be prevented from being completely absorbed. Under these circumstances the proper method of studying the effect of adrenalin upon absorption appears to be by intravenous application. This method was employed by us in most of our further experiments, which we carried out mostly on rabbits, the adrenalin being injected into the ear veins.

We shall report first our experiments with strychnin. A few abbreviated protocols will illustrate our results.

Experiment 5. Rabbit I. (control, 1625 grams) received subcutaneously strychnin nitrate 0.505 mg. per kilo. After thirteen minutes characteristic tetanus; survives. Rabbit II. (2000 grams) received 1 c.c. adrenalin into the ear vein; three minutes later

subcutaneous injection of strychnin 0.55 mg. per kilo. Watched for three hours, animal somewhat prostrated, no spasm, no reaction, even after handling.

The difference between the two animals in this experiment is quite striking. While the control with 0.505 mg. strychnin per kilo had a tetanus after thirteen minutes, there was no reaction in the adrenalin animal, though the dose of strychnin was even larger, 0.55 per kilo.

Experiment 6. Rabbit I. (1500 grams) received subcutaneous injection of strychnin nitrate 0.6 mg. per kilo. Tetanus, opisthotonos after six minutes and death five minutes later. Rabbit II. (2500 grams) received 1 c.c. adrenalin into ear vein; four minutes later strychnin subcutaneously 0.6 mg. per kilo. Some slight temporary prostration. Tetanus after forty minutes. Recovered in a few minutes.

Control had tetanus in six minutes, and died soon after; adrenalin animal had tetanus after forty minutes and recovered soon. In both, strychnin 0.6 mg. per kilo, and adrenalin only 1 c.c. to 2500 grams weight.

Experiment 7. Rabbit I. (control, 1500 grams) injected subcutaneously 0.6 mg. strychnin nitrate per kilo. After twenty-four minutes tetanus and death. Rabbit II. (1225 grams) received 1 c.c. adrenalin into ear vein; twelve minutes later injected subcutaneously strychnin nitrate 0.72 mg. per kilo (by miscalculation). Marked adrenalin prostration, watched for one hour, handled roughly, but no convulsion. Rabbit III. (2500 grams), 6.03 P.M., received 1 c.c. adrenalin in ear vein; four minutes later (6.07 P.M.) 1 c.c. adrenalin subcutaneously; five and one-half minutes later (6.12½ P.M.) strychnin nitrate subcutaneously 0.72 mg. per kilo; six and one-half minutes later (6.19 P.M.) once more 1 c.c. adrenalin intramuscularly. For fifty-six minutes there was neither prostration nor noteworthy hypersensitiveness. At the end of this time (7.08 P.M.) a few slight convulsions made their appearance. In five minutes they passed off and the animal recovered fully.

In this experiment the control with only 0.6 strychnin per kilo had tetanus, and died in twenty-four minutes. Of the two adrenalin animals both had 0.72 mg. strychnin per kilo; one had no con-

vulsions at all, and in the other the convulsions were much delayed, were mild, and lasted only a few minutes, the animal recovering completely.

Other illustrations are hardly necessary. The experiments show clearly that an intravenous injection of a comparatively moderate dose of adrenalin is capable either of completely overcoming of distinctly delaying and greatly mitigating the effects of a surely fatal dose of strychnin. For the mitigating effect of adrenalin it is not necessary to apply it directly to the tissues; it is sufficient if a comparatively moderate dose is brought to the tissues through the circulation. In fact, this mode of administration is much more effective; for neither in our experiments on the frogs, nor in the experiments of Exner on rabbits and guinea-pigs, did the hypodermic or the intraperitoneal injection bring out such striking results as we obtained by the intravenous method.

Our experiments further conveyed the impression that the prostrating effect of adrenalin was not entirely without influence upon the toxic effect of strychnin. When the animal was small an intravenous injection of 1 c.c. of adrenalin would cause marked prostration. In such animals there were no convulsions at all. And in nearly all adrenalin animals there has been very little hyperesthesia preceding the delayed convulsions. Nor did any amount of handling have any marked influence in bringing on the tetanus, as was invariably the case with the control animals. On the other hand, we may also state that the prostration due to the adrenalin was in many cases unmistakably mitigated and shortened by ineffective doses of strychnin.

While our experiments on frogs as well as on rabbits show distinctly that the essential part of the mitigation of the effects of strychnin by the administration of adrenalin cannot be due simply to a mutual neutralization of the effects of these substances upon the spinal cord, we will have to admit that some degree of such neutralization actually takes place when an injection of strychnin follows that of adrenalin. As our chief object was to test the hypothesis that the delaying effect of adrenalin is due to its influence upon some of the factors of the mechanism of absorption, we deemed it advisable to study the effect of adrenalin upon the

absorption of a substance which gives characteristic signs, but which is otherwise innocuous to the tissues and functions of the animal body. We decided upon such a course long before we knew of the experiments of Exner. Such a substance we found in fluorescein. It stains the skin and mucous membranes yellow, also the fluids and tissues of the body (except the nervous system), but is otherwise perfectly harmless.

Fluorescein is the mother substance of eosin. It is slightly acid, and gives with alkalies easily soluble salts. In concentrated solutions it is dark red without fluorescence. When diluted, it is at first yellowish-red, and in still further dilution it becomes yellow, and shows a brilliant yellowish-green fluorescence. The fluorescence is still recognizable in a dilution of 1 : 2,000,000 (Ehrlich). Our first experiments were made with the stain kindly given to us by Professor Ehrlich,[1] probably a potassium salt. For the further experiments the salt was prepared by the addition of sodium hydrate to Gruebler's fluorescein.

The several series of experiments, the results of which we will now report, were carried out by subcutaneous and intravenous injections of that substance.

In the first series of experiments, the adrenalin as well as the fluorescein, were administered by subcutaneous injection into different parts of the body. We shall illustrate the results by a few protocols.

Experiment 8. Rabbit I., brown, subcutaneous injection of adrenalin 2 c.c. Eleven minutes later injected into the opposite side 20 c.c. 5 per cent. fluorescein. Twenty-one minutes after last injection conjunctivæ, gums and ears yellow. Forty-two minutes after injection appearance of Ehrlich's line, later the entire pupil greenish. Rabbit II., brown (control), injected subcutaneously 20 c.c. 5 per cent. fluorescein. After eight minutes ears, gums

[1] In fact the stimulus to the entire work was given by an observation made September, 1908, in Ehrlich's Institute for Experimental Therapeutics, Frankfurt. Professor Ehrlich wished to show the well-known line on the cornea brought out by a subcutaneous injection of fluorescein into a rabbit. The experiment failed; the rabbit, which received a large dose of the stain, did not even become yellow. One-half hour previous to this experiment I had injected intravenously into the very same rabbit a large dose of adrenalin for the purpose of bringing out the effect of the removal of the superior cervical ganglion upon the pupil. It was then that the suggestion occurred to me that suprarenal extract possibly affects absorption.—S.J.M.

and conjunctivæ yellow; five minutes later all very yellow; twenty minutes after injection distinct Ehrlich's line and the entire pupil greenish.

The yellow color of the skin and mucous membranes, as well as the greenish color of the pupils, was more intense in the control than in the adrenalin animal.

Experiment 9. Rabbit I., white, 1500 grams; subcutaneous injection of 2 c.c. adrenalin; twelve minutes later 1.5 c.c. 5 per cent. fluorescein; conjunctivæ and gums yellow in fifteen minutes, ears and anus in twenty-seven minutes after last injection. No Ehrlich's line and no greenish pupils. Rabbit II., gray, 1375 grams, control, injected subcutaneously 1.5 c.c. 5 per cent. fluorescein. Conjunctivæ, gums, ears and anus yellow fifteen minutes after injection. No Ehrlich's line; pupils diffusely greenish.

There was a delay also in this experiment, although considerably less marked than in the previous one.

A certain delay was also observed when the fluorescein was injected into the peritoneal cavity, as can be seen from the following experiment:

Experiment 10. Rabbit I., brown, injected subcutaneously 2 c.c. adrenalin; fourteen minutes later injected into the peritoneal cavity 10 c.c. 5 per cent. fluorescein. Conjunctivæ, gums and anus yellow seven minutes after injection, ears and Ehrlich's line eleven minutes; pupil greenish fifty-four minutes after injection. Rabbit II., brown, control; 10 c.c 5 per cent fluorescein injected into peritoneal cavity. Conjunctivæ and gums yellow three minutes after injection, ears eight minutes, anus nine minutes, Ehrlich's line fourteen minutes, and the pupils distinctly greenish eighteen minutes after injection.

In every regard there was a moderate delay in the adrenalin animal, except in the appearance of Ehrlich's line, which appeared in this animal even a few minutes earlier than in the control.

The delay which occurred when the adrenalin was administered subcutaneously was, however, variable in degree and never so pronounced as in some cases when the adrenalin was administered intravenously; here the delay amounted to nearly a complete sup-

pression of the signs. The following experiment is a good illustration :

Experiment 11. Rabbit I., large, brown, injected subcutaneously 5 c.c. of 5 per cent. fluorescein. Conjunctivæ and ears yellow after ten minutes, gums, skin of neck and anus after fifteen minutes, pupil greenish after thirty-five minutes, Ehrlich's line after forty minutes. Rabbit II., brown, injected subcutaneously 2 c.c. of adrenalin ; two minutes later injected subcutaneously into other side 5 c.c. of 5 per cent. fluorescein. Conjunctivæ yellow (very faint) twelve minutes after last injection, gums twenty-five, anus twenty-seven, skin of neck thirty, ears thirty-three, Ehrlich's line thirty-three, and pupil greenish thirty-eight minutes after injection of fluorescein. Rabbit III., large, black, injected into ear vein 1 c.c. of adrenalin ; three minutes later injected subcutaneously 5 c.c. of 5 per cent. fluorescein. Twenty-seven minutes after last injection ears yellow (very faintly), after eighty-eight minutes conjunctivæ ; gums and anus very faintly yellow ; skin of neck very faintly yellow after two hours. Ehrlich's line and greenish pupils never appeared.

While there was also a moderate delay in Rabbit II. (adrenalin subcutaneously), there was nearly a complete suppression of any effect from 5 c.c. of 5 per cent. fluorescein in the animal which received adrenalin into the ear vein.

However, even with intravenous administration of adrenalin the result was not always so striking as in the foregoing experiment. In fact, we had one experiment in which adrenalin was administered first intravenously and a few minutes later subcutaneously, in which, nevertheless, the retarding effect was very moderate.

Experiment 12. Rabbit I., brown, 1750 grams ; injected into the ear vein 1 c.c. adrenalin ; eleven minutes later injected subcutaneously 1 c.c. adrenalin ; four minutes after last injection of adrenalin a subcutaneous injection of 4.1 c.c. of 5 per cent. fluorescein was given ; ten minutes after injection of fluorescein very faintly yellowish tint of conjunctivæ and anus ; thirteen minutes ears moderately yellow ; seventeen minutes gums moderately yellow ; twenty minutes skin of neck yellow ; twenty-five minutes definite Ehrlich' line, and soon after pupil greenish. Rabbit II., brown, 1250 grams ; injected subcutaneously 3.75 c.c. of 5 per cent. fluo-

rescein. Eight minutes after injection conjunctivæ and anus definitely yellow; after eleven minutes ears and skin of neck yellow; fifteen minutes gums yellow and definite Ehrlich's line, soon after pupils greenish.

The color in each place was in the beginning unmistakably more intense in the control than in the adrenalin animal. The difference, however, gradually disappeared. While even in this experiment there was some delay, and also some difference in the intensity of the color, the entire difference was insignificant, and could not compare with the results obtained in most of the experiments of this series.

This series of experiments, then, brought out the following results: A subcutaneous injection of a large dose of adrenalin (2 c.c.) retards and diminishes the coloring of skin and mucous membranes, due to a subsequent subcutaneous injection of fluorescein. The retarding effect is much stronger when the adrenalin is injected intravenously, the result being sometimes nearly equal to a complete suppression of the appearance of the color. The degree of the retarding influence, however, is variable, and for the present, at least, nothing can be stated as regards the cause of this variability.

All the experiments hitherto recorded agree in the general result that a previous administration of adrenalin retards the appearance and reduces the intensity of the effects of a substance subsequently injected subcutaneously. This retardation and mitigation can hardly be due to a chemical interaction between the adrenalin and the other substances, since the effect is the same, in rabbits at least, whether adrenalin and the other substances come into direct contact or are injected into different parts of the body. Neither could it be due to some biologic neutralization, since even the appearance of the color of such an innocuous substance as fluorescein is retarded by a previous administration of adrenalin.

We have stated above that the retardation might be due to some impairment in the mechanism of absorption. We have to remember, however, that in the chain of events between the injection of strychnin and the occurrence of convulsions, or between the injection of fluorescein and the appearance of the color in the skin and

mucous membranes, these substances, besides their absorption into the blood, have to be transuded into the lymph again and then taken up by the different tissue cells before the signs or symptoms can make their appearance. Now the retardation might be due not to a lowering of absorption, but to some disturbance in some other parts of that chain, for instance, to a disturbance in the lymph secretion. Or the retardation might be due even to greater elimination by the specific organs, as the liver or kidneys, thus preventing the rapid accumulation of the necessary minimum dose within the blood. We might call to mind here that, according to Langley,[1] the injection of suprarenal extract causes, indeed, some increase in the secretion of bile.

To throw better light upon the questions raised here we have carried out a series of experiments in which, in the first place, the question of absorption was studied more directly by the following method: A cannula was inserted into the carotid artery; some blood was taken regularly every two, three or more minutes into small test tubes and permitted to clot and separate the serum. When a sufficient quantity of fluorescein was injected subcutaneously the serum showed a distinct fluorescence varying in degree according to the quantity and according to the interval after the injection. In the first period after an injection the fluorescence of the serum is the stronger the later the blood is taken; in the second period it is the reverse: the later the blood is taken the less fluorescence is present. Adrenalin causes rapid clotting of the blood, and it was more convenient to obtain the blood directly from the artery, since the cannula frequently became obstructed by clots. We shall now again illustrate our results by some greatly abbreviated protocols.

Experiment 13. Rabbit I., brown, 1500 grams; morphin subcutaneously; cannula in carotid artery; adrenalin 1 c.c. into ear vein; eleven minutes later 1 c.c. adrenalin subcutaneously; five minutes later injected subcutaneously 15.5 c.c. of 5 per cent. fluorescein. Blood taken first every minute, then every two minutes. Rabbit II., brown, 1500 grams; morphin; cannula in carotid; injected subcutaneously 1.5 c.c. of 5 per cent. fluorescein; blood taken as above.

[1] Loc. cit.

Serum of the tubes from both animals compared. In control fluorescence after one minute; in adrenalin after two minutes, distinctly fainter. Fluorescence of serum taken from adrenalin animal after eleven minutes not perceptibly stronger than that of the serum from the control taken one minute after the injection of fluorescein.

Experiment 14. Rabbit I., white, 1250 grams; morphin; carotid artery; 1 c.c. adrenalin into ear vein; after nine minutes 1 c.c. adrenalin subcutaneously; two minutes later subcutaneous injection 1.25 c.c. of 5 per cent. fluorescein; blood taken. Rabbit II., brown, 1625 grams; morphin; carotid; injected subcutaneously 1.5 c.c. of 5 per cent. fluorescein; blood taken.

In both fluorescence was present in the blood (serum) taken one minute after injection, but in that of the adrenalin animal the fluorescence was faint. The fluorescence of the serum taken after three minutes from the adrenalin animal is equal to that taken after one minute from the control; and the serum of the adrenalin animal taken thirty minutes after injection was equal to that of the control taken fourteen minutes after the injection.

In a few experiments, in which at the beginning there was distinctly less fluorescence in the serum of the adrenalin animal, the relation soon became reversed, so that about twenty minutes after injection there commenced to be more fluorescence in the serum of the adrenalin animal than in the control. The reason for it apparently was that while in the control the absorption of the greatest part of the injected fluorescein took place in the first few minutes, and the accumulated coloring substance within the blood began to disappear by transudation and elimination, both these processes—absorption and elimination—were delayed in the adrenalin animal, while the fluorescein continued to be slowly absorbed, thus gradually increasing the amount of the coloring matter within the blood, since its elimination from the blood was also delayed.

In order to rule out at least one of these factors—the continuation of absorption—in a few experiments the injections were made into one of the hind legs, and some time after the injection the legs were tightly constricted above the injected stain, thus preventing its further absorption. The following protocol is an example of such an experiment:

Experiment 15. Rabbit I., black, very young; 900 grams; morphin; carotid artery; ½ c.c. adrenalin into ear vein; two minutes later ½ c.c. of 2 per cent. fluorescein into right hind leg; blood regularly taken. Ten minutes after injection of fluorescein leg ligated above site of injection; animal killed half an hour after injection. Rabbit II., black, very young; 900 grams; morphin; carotid artery; injected ½ c.c. of 2 per cent. fluorescein into the right hind leg; blood regularly taken. Ten minutes after injection leg ligated above site of injection. Animal killed half an hour after injection.

In these animals there was no further absorption ten minutes after injection. The blood specimen of the adrenalin animal taken twenty-nine minutes after injection of fluorescein contained less fluorescence than the specimen from the control animal taken four minutes after injection.

By this series of experiments, then, it was established beyond a doubt that an intravenous injection of adrenalin retards in a greater or less degree the absorption into the blood of fluorescein administered by subcutaneous injection. We should add that in these experiments, too, the degree of impairment of absorption varied in individual animals.

In our studies on the blood of adrenalin animals we made a few minor observations which we might mention here briefly. In the first place, we can confirm the statement of Vosburgh and Richards[1] that the blood of adrenalin animals clot more readily than that of the controls. We noted, however, that the clots of these animals contracted a good deal more slowly, and the serum separated a good deal later than in the controls. It was also noted that the blood of adrenalin rabbits manifested a greater inclination to hemolysis than the blood of their normal mates.

We have, then, established that adrenalin impairs in some way the absorption from the tissues. What structures become affected? Exner assumes that it is the absorption by the lymphatics which becomes impaired. He bases this assumption on his experiment in which the absorption of an emulsion of paraffin was somewhat im-

[1] American Journal of Physiology, 1903, vol. xi. p. 30.

paired after a preceding intraperitoneal injection of adrenalin. Such an experiment, however, justifies only the conclusion that the lymphatics are impaired also, but not that the absorption by the bloodvessels is unaffected.

In our experiments with fluorescein we have repeatedly established that already one minute after a subcutaneous injection there was a definite fluorescence in the serum of the blood. Such a very rapid absorption into the blood could not possibly take place through the lymphatics. We take, therefore, the stand that adrenalin affects in some way the absorption through the bloodvessels, and, judging by the experiments of Exner, probably, also the absorption through the lymphatics.

What is the influence of adrenalin upon elimination from the blood? It was mentioned above that in some experiments there seemed to be at certain periods more fluorescence in the blood of the adrenalin animal than in that of the control. The conclusion was unavoidable that in these cases there has been in the adrenalin animal a delay in the elimination of the absorbed coloring matter. Similar observations were made when the color of the skin, mucous membranes, etc., was taken as an indication of the presence of fluorescein in the animal body. It was sometimes observed that the adrenalin animal was still yellow, while the control had lost all traces of the stain.

In a few instances such observations were made also on frogs when the adrenalin was injected in one place and fluorescein into another place. Aside from the remarkable change of the color of the skin, the pupils of these animals became emerald green. This characteristic appearance was noticed in a few instances to persist much longer in the adrenalin animal than in the control. However, in all these cases the fluorescein was injected subcutaneously, and any retardation in elimination from the animal might have been actually due only to a delayed absorption into the blood, and not to a delay of elimination from the blood.

To study the elimination from the blood it was necessary to have the adrenalin animal and the control on the same footing as regards absorption. We have therefore carried out a series of experiments on rabbits in which the fluorescein also was administered intraven-

ously, and either the time of the disappearance of the color from the skin, etc., was studied, or the sera of both animals were compared as regards the degree of their fluorescence. Many experiments had to be made in this series before we could obtain satisfactory results. The injected quantity of fluorescein was either too large or too small; in either case the differences were not sufficiently striking.[1] We had, however, quite a number of successful experiments which left no doubt that the elimination of fluorescein from the blood was in a greater or less degree retarded in the adrenalin animal. The following examples will illustrate:

Experiment 16. Rabbit I., brown, injected into right ear vein 0.65 c.c. adrenalin; three minutes later into left ear vein 1.5 c.c. of 5 per cent. fluorescein; one hundred and thirty minutes later pupils green; conjunctivæ, gums, anus, skin of neck, etc., still very yellow. Rabbit II., brown; 1.5 of 5 per cent. fluorescein into right ear vein. One hundred and twenty minutes later all parts of the body which had been very yellow showed practically no trace of the color.

Experiment 17. Rabbits I., II., and III., gray, 1000 grams each, received into right ear veins 0.5 c.c. adrenalin, and seventeen minutes later 1 c.c. of 5 per cent. fluorescein into the left ear veins. Rabbit IV., gray (control, 1000 grams), received into the ear vein 1 c.c. of 5 per cent. fluorescein. At first control more yellow all over; two hours later adrenalin animals showed more yellow color than the control. One adrenalin animal died. Two hours and forty minutes after injection blood taken from two adrenalin animals and from the control. Serum of control definitely less fluorescent than that of adrenalin animals.

Experiment 18. Rabbit I., brown, 1250 grams; morphin; carotid artery; 0.3 c.c. adrenalin into ear vein; twenty minutes later 0.2 c.c. more adrenalin into ear vein; nine minutes later 1 c.c. of $\frac{1}{10}$ per cent. fluorescein into other ear vein; blood taken at regular intervals. Rabbit II., brown, 1375 grams; morphin; carotid artery; injected into ear vein 1 c.c. of $\frac{1}{10}$ per cent. fluorescein; blood taken at regular intervals.

[1] By accident we had at the time we were carrying out this series only young, small rabbits at our disposal. Only small doses of adrenalin could be administered, and that only in fractions; and even so we lost many animals from pulmonary edema.

A comparison of the blood specimens shows that the serum of the adrenalin animal contains definitely more color and fluorescence than that of the control. Adrenalin blood taken after sixty-six minutes shows as much color and fluorescence as the control blood taken after thirty minutes.

The series of experiments in which the fluorescein was injected intravenously definitely brought out the fact that in the adrenalin animal the color disappears from the blood much later than in the control. The same is true also of the color of the skin and mucous membranes: it disappears later in the adrenalin animal. However, it was also seen that after there was no more color in the skin, etc., in either of the animals, there was still fluorescence in the blood of both animals, but again more in the adrenalin animals.

We may add that in intravenous injection of fluorescein there was in the adrenalin animal at first a distinct retardation in the appearance of the color in the mucous membranes, and especially in the skin. We can interpret this only by assuming that there was a retardation either in the secretion of the lymph or in the taking up of the color by the tissue cells, or in both processes.

The delayed elimination of any substance from the blood may be due to a retardation in the elimination of this substance by the kidneys, the liver, or both, and to a degree also to a delay in the reabsorption of the substance from the tissues and the lymph. That the reabsorption, indeed, is delayed would seem to be supported by the fact that the coloration of skin and mucous membranes persists perceptibly longer in animals which received an intravenous injection of adrenalin. We have not, however, studied this problem by direct experiments.

The question of retardation of elimination by the kidneys and the liver we have already studied in numerous experiments; but we are not yet ready to report our results in this paper. The conditions are quite complicated and a good deal more experimentation will have to be done before definite statements can be made. Especially is the frequent pathological condition of the kidneys in apparently normal animals quite a disturbing factor in the study of that problem. We had, for instance, animals in which the kidneys of the adrenalin individual were perfectly green (fluorescein),

while that of the control showed no staining at all, on account of the fatty degeneration of the kidneys of the control animal. We hope, however, in the near future to be able to offer some positive results in regard to that vexed problem.

A subject of greater concern was to us the question whether the normal transudation from the blood into the surrounding tissue spaces—the formation of lymph—is affected by the administration of adrenalin. We have already stated above that even in the intravenous application of fluorescein the coloring of the skin and mucous membranes was perceptibly retarded by a previous administration of adrenalin, which can mean only that the passage of the stain from the blood into the tissues occurred with less freedom than in normal animals. However, the chief obstacle might have been not in the stain traversing the capillary wall, but in its reaching the cells, the "absorption" into the epithelia.

Our attempt to study directly the appearance of the stain in the lymphatics of the mesentery was not very successful; we were not sure enough that the lymphatics in the adrenalin animal showed the stain later than those of the control.

The following method, however, brought satisfactory evidence that also the transudation through the capillaries is notably affected by an administration of suprarenal extract. The animals received intraperitoneal injections of sodium chlorid (0.9 per cent.), and then every few minutes small quantities of it were withdrawn and tested for fluorescence. The following abbreviated protocols of such experiments will illustrate our results:

Experiment 19. Rabbit I., black, 900 grams: ether; 50 c.c. salt solution (0.9 per cent.) into the peritoneal cavity; 0.4 c.c. adrenalin into right ear vein; nine minutes later 0.3 c.c. adrenalin hypodermically; three minutes after last injection injected into left ear vein 1 c.c. of 2 per cent. fluorescein; every few minutes salt solution taken from peritoneal cavity. Rabbit II., black, 900 grams; ether; 50 c.c. salt solution (0.9 per cent.) into peritoneal cavity; injected into ear vein 1 c.c. of 2 per cent. fluorescein; salt solution taken from peritoneal cavity at regular intervals.

Result of comparison: Solution taken from adrenalin animal fifteen minutes after injection of fluorescein is equal in color and

fluorescence to that taken from the control nine minutes after injection.

Experiment 20. Rabbit I., white, 1000 grams; ether; 0.6 adrenalin into right ear vein; twelve minutes later 25 c.c. salt solution into peritoneal cavity, and two minutes after ½ c.c. of 2 per cent. fluorescein into left ear vein. Tested fluid regularly taken from peritoneal cavity.

Rabbit II., white, 1000 grams; ether; 25 c.c. salt solution into peritoneal cavity, and one minute after ½ c.c. of 2 per cent. fluorescein into ear vein; tests regularly taken.

Result: Solution taken from the peritoneal cavity of adrenalin animal twenty-one minutes after injection of fluorescein is not as fluorescent as the solution taken from the control eight minutes after the injection.

In order to increase the transudation of fluorescein, and also to exclude the threatening factor of nephritis in one of the animals, some experiments were carried out on previously nephrectomized animals.

Experiment 21. Rabbit I., white, 1000 grams; ether; vessels of both kidneys ligated through lumbar incision; 0.5 c.c. adrenalin into right ear vein; after eight minutes 0.4 adrenalin intramuscularly; 25 c.c. salt solution into peritoneal cavity; three minutes after last injection of adrenalin, injected into ear vein ½ c.c. of 2 per cent. fluorescein; tests regularly taken. Rabbit II., 1000 grams; ether; lumbar nephrectomy; 25 c.c. salt solution into peritoneal cavity; ½ c.c. of 3 per cent. fluorescein into ear vein; tests regularly taken.

Result: Test taken from adrenalin animal twenty minutes after injection equal in color and fluorescence to that taken from control ten minutes after injection of fluorescein.

Experiment 22. All particulars as in foregoing experiment, except weight of rabbits, 1600 grams each; 1 c.c. of 2 per cent. fluorescein was given and 0.7 c.c. adrenalin.

Result: Test from adrenalin animal thirty minutes after injection shows as much color and fluorescence as that taken from the control fifteen minutes after injection of fluorescein.

These series of experiments left no doubt that the fluorescein

transudes from the blood into the peritoneal cavity distinctly more slowly in animals which had previously received intravenous injections of adrenalin than in normal animals.

From our experiments it appears probable that the transudate in adrenalin animals is poorer in proteids than that of the control, a fact which could be utilized in the study of the question of the effect of adrenalin upon the formation of lymph. However, in such a case the amount of the proteids present in the peritoneal fluid of each animal would have to be established before the injection of adrenalin, which we have not done.

It is worth recording that when the peritoneal fluid became somewhat richer in proteid content in the adrenalin animal it became so completely clotted that the test tube could be inverted. Adrenalin apparently hastens clotting even in transudates. We shall recur to it in later studies.

We shall record here an experiment reported by Wessely[1] a few years ago which also demonstrates the retarding effect of suprarenal extract upon the process of transudation. He injected suprarenal extract (suprarenin, v. Fürth) into the subconjunctival tissue of one eye of a rabbit, and after fifteen minutes opened by puncture the anterior chambers of both eyes. On the normal side the anterior chamber filled up again after ten to fifteen minutes, while on the adrenalin side it did not attain its natural state, even after thirty minutes. The aqueous humor on the adrenalin side was also poorer in proteids than on the normal side.

Our several series of experiments have established two essential facts: that suprarenal extract retards absorption from the tissues into the blood, and retards transudation from the blood into the tissues. In the process of transudation no other capillaries are concerned than those of the blood. We have given above our reasons for the belief that suprarenal extract affects, in the first place, the absorption by the bloodvessels, and probably also the absorption by the lymphatics. In short, suprarenal extract affects the capillaries in such a manner that the passage of fluid through their walls in either direction is impaired, retarded.

[1] Bericht der Ophthalmologischen Gesellschaft, Heidelberg, 1900, p. 69.

What is the nature of this impairment? As the rise of blood pressure is the best-known property of the suprarenal extract, and, as the intracapillary pressure is a more or less potent fact in the production of lymph, that is, in the processes of transudation and absorption, the suggestion presents itself that the impairment of these processes by the suprarenal extract has something to do directly with the blood-pressure raising property of the extract. A closer analysis of the concerned facts will show, however, that such an assumption is untenable.

In the first place, the rise of blood pressure could not be the cause of the retardation of the two opposing processes at the same time. For instance, if the rise of blood pressure would cause a rise of the intracapillary pressure it would, indeed, impair absorption, but then it should rather favor transudation. Or if the intracapillary pressure would be diminished, as is probably the case when the rise of blood pressure is due to a strong constriction of all the small arteries, transudation would be retarded; but then absorption would be favored instead of being impaired. Besides, in nearly all experiments the impairment of absorption and transudation through intravenous injection of adrenalin was taking effect long after the effect of the blood pressure had passed off, the rise in pressure usually lasting only a few minutes.

Neither could the impairment be due to chemicophysical changes in the blood and lymph, since such changes again could be effective only for one of the opposing processes, but not for both at the same time and in the same manner.

The theory which we are going to offer in explanation of retardation of absorption and transudation, which is caused by the administration of suprarenal extract, consists in the assumption that the extract decreases the permeability of the endothelial wall of the capillaries, and is based upon a view of the vital nature of the changes of this permeability brought forward by one of us in another paper.[1] (In fact, it was this view which gave the stimulus for the present investigation.)

This view is as follows: 1. The endothelia, like all organized

[1] S. J. Meltzer, "Edema." Harrington Lectureship, University of Buffalo, 1903.

matter, have pores; whether these pores run in a straight line, or whether the fine canals connecting both surfaces of the endothelial cells run in a tortuous course, is immaterial for our purpose. 2. The endothelia are living tissues, and possess irritability and contractility. We know now that they are phagocytes, which, of course, presupposes contractility. These two premises are generally acknowledged facts. If these premises are true, the following ought to be true, also: both surfaces of the endothelia are connected by pores, each of which is surrounded by contractile tissue. But as contractile tissue is sometimes more and sometimes less tonically contracted, and the tonicity can be increased and decreased by various stimuli, we have to assume that the tissue around the pores is sometimes more, sometimes less contracted; that means that the lumina of the pores change according to the state of the tonicity of the endothelial tissue and according to the stimulation to which it is exposed at different times. Accordingly, the endothelial pores are fine canaliculi surrounded by contractile sphincters which control the size of their lumina. In other words, the contractility of the endothelia controls their permeability. The permeability of the living vascular endothelia is therefore essentially different from the physical permeability of dead animal membranes; it is a vital phenomenon. It is obvious that no matter what other factors control transudation and absorption of lymph, the vital permeability of the vascular endothelia will influence these processes to a considerable degree. Whether the essential factor is the intracapillary blood pressure (Ludwig, Starling) or the osmotic pressure within the tissue cells and the lymph spaces (v. Koranyi, J. Loeb), or some vital activity of the tissue cells (Lazarus-Barlow, Asher), or whether all these factors work together in the processes of absorption and transudation of lymph (Meltzer), the size of the lumina through which the interchange of the fluids takes place will necessarily influence the end-result; and the size of the lumina depends upon a changeable, vital factor—the contractility of the endothelial cell. Whether it is necessary to assume that the endothelial wall has still another vital activity, a secretory function (Heidenhain, Hamburger), that question we shall not discuss here. We shall only point out that in contradistinction to the secretory theory of

lymph in our assumption no new "vital" property is attributed to the vascular endothelias; irritability and contractility are accorded to them by all writers.

To recapitulate briefly: the endothelial pores, through which, probably, the exchange of fluid in the processes of transudation and absorption takes place, are surrounded by a contractile tissue which is capable of changing the lumen of these pores, thus influencing the rate of these processes.

In normal processes the degree of contractility, the tonicity of the endothelia is determined by the metabolic processes within the endothelia themselves, as well as by the nature of the substances with which they come into intimate contact, on the blood side as well as on the lymph side of the blood capillaries.

The question that presented itself to us now was whether there are not substances by means of which we can, at will, increase and decrease the tonicity of the endothelial protoplasm, thus increasing and decreasing the vital permeability of the endothelia, and hindering or facilitating the processes of transudation and absorption. We thought of the suprarenal extract as such a substance; hence the present series of experiments.

Now we have established by these experiments that the administration of adrenalin, indeed, retards transudation as well as absorption of some foreign substances through the capillary walls. We are therefore ready to explain these retardations by the assumption that suprarenal extract increases the tonicity of the endothelial protoplasm, and thus decreases the vital permeability of the vascular wall.

That the extract is capable of increasing the tonicity of contractile tissues we know from its effects upon the striated and smooth muscle fibers. Oliver and Schaefer[1] found that the effect of the suprarenal extract upon striated muscle is to prolong its contraction. The rise of blood pressure, which is caused by the effect of the extract upon the smooth muscle fibers of the arteries, lasts for many minutes, and it was shown[2] that the contraction of the blood-vessels of the rabbit's ear can be considerably prolonged by section

[1] Journal of Physiology, 1895, vol. xviii. p. 230.

[2] S. J. and Clara Meltzer, American Journal of Physiology, 1903, vol. ix. p. 252.

of the cervical sympathetic nerve. Furthermore, the extract causes also a dilatation of the pupil, apparently by stimulating its dilator, which, according to Langley and Anderson,[1] is a "radial contractile substance," although, as they state, they could not satisfy themselves "that it has the form of ordinary unstriated muscular tissue." It was shown further[2] that when the superior cervical ganglion was removed (in rabbits and cats) the dilation of the pupil may last a few hours. The same authors[3] have stated recently that in frogs subcutaneous injection or instillation of small doses of adrenalin causes normally a dilatation of the pupil which lasts more than twenty-four hours. Suprarenal extract possesses, then, the property of increasing the tonicity of contractile tissues, which effect seems to last the longer, the less organized, if we may say so, the contractile tissue is. We wish to bring out this point especially on account of the popular view that the effect of suprarenal extract is only of very short duration. This view is based upon the experience with the effect of the extract upon blood pressure. In our experiments on absorption and transudation the retarding effect of adrenalin was present long after its injection. We do not know exactly how long the retarding effect lasts, but it certainly lasts a good deal longer than the effect upon the blood pressure. However, we doubt greatly whether it lasts as long as the effect of the extract upon the pupil, which, as stated above, may last even longer than twenty-four hours.

Our theory, then, in brief is as follows: Suprarenal extract causes an increase of the tonicity of the contractile protoplasm of the endothelia of the blood capillaries and lymphatics. This increase in tonicity narrows the lumen of the pores and decreases the facility for the interchange between the blood and the tissue fluid (lymph). In other words, the extract decreases the vital permeability of the capillary wall; hence the retardation of absorption and transudation.

The following is a brief *résumé* of our results:

1. Intravenous injections of suprarenal extract retards invariably the processes of absorption and transudation.

[1] Journal of Physiology, 1902, vol. xiii. p. 554.
[2] S. J. and Clara Meltzer, American Journal of Physiology, 1904, vol. xi. p. 28.
[3] Ibid., p. 450.

2. Subcutaneous injections also often show a retardation of these processes; the effect, however, is neither strong nor constant.

3. In frogs the retardation of absorption of some substances was recognizable only when adrenalin was previously mixed with that substance, or when both substances were injected into one and the same lymph sac.

4. It is assumed that the suprarenal extract increases the tonicity of the protoplasm surrounding the pores of the endothelia of the capillaries, hereby reducing the facility for the interchange between the blood and the tissue fluid.

DISCUSSION.

DR. W. GILMAN THOMPSON: I was much impressed by Dr. Meltzer's report of the action of adrenalin upon the kidneys. I have often used adrenalin intravenously in man in cases where infusions were being given and I have never observed the slightest effect either upon the quantity or composition of the urine, so I do not think this remedy, in therapeutic doses, at least, has any influence upon the kidney; it is possible, however, that it may, when used experimentally, because of its more continuous employment.

DR. HARE: A point which strikes me as being of interest is the action of adrenalin as compared with that of other remedies. Our conception has been that its action is quite brief, so it is not clear to me how it can be used to prolong the effect of other remedies unless it is given in repeated doses.

Another point of interest is, that I have been impressed by the fact that the local application of adrenalin increases the danger of infection. I have seen a number of cases this winter in which the ischemia produced by the local application permitted infection to occur; for instance, when sprayed on the tonsils the resulting ischemia seemed to permit the rapid involvement of the neighboring glands. I have also seen other cases where the adrenalin was given hypodermically, and sloughs occurred which were due, I suppose, to the same cause.

DR. MELTZER: Dr. Hare raises the point that the action of adrenalin is usually very brief. This view is taken from the knowledge of the effects of suprarenal extract upon the general blood pressure. Here, indeed, the effect lasts only a few minutes. But the extract produces many other effects upon the various organs of the body. It causes, for instance, a dilatation of the pupil. And we have shown recently that if the superior cervical ganglion has been

removed, a subcutaneous injection of adrenalin, which produces no effect upon the blood pressure, will cause a dilatation of the pupil which can last for hours. To-day we have described experiments which demonstrate again a new effect of the suprarenal extract: it retards absorption and transudation. That this effect lasts a good deal longer than the effect upon the blood pressure can serve only as evidence that the effect upon absorption and transudation is not simply a secondary result of the effect of the extract upon blood pressure.

THE CULTIVATION OF THE SURRA TRYPANOSOME OF THE PHILIPPINES.

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ALTHOUGH the *Trypanosoma evansi*, the cause of surra, was discovered by Evans in India as early as 1880, and the disease itself has been studied exhaustively by Lingard (1893-1896), relatively but little attention has been given to the parasite itself. Koch while in German East Africa in 1898 described the disease prevailing in that region as surra, because he was of the belief that surra and nagana, or the tsetse-fly disease, were identical. Bruce himself, in his work upon the latter disease in 1894, inclined to the view of a possible identity of the trypanosome studied by him with that of Evans. Various other workers have held similar opinions, and even as late as last year Musgrave and Clegg[1] conclude that surra, nagana, mal de caderas, and probably dourine are the same disease, and that all are caused by *Trypanosoma evansii*.

The immunity experiments of Laveran and Mesnil[2] and those of the late Professor Nocard as reported by Vallée and Carré,[3] however, show quite conclusively that surra, nagana, and mal de caderas are distinct entities notwithstanding the marked similarity in the symptoms of these diseases. Moreover, the difference in the mor-

[1] Bulletin No. 5, Bureau of Government Laboratories, Manila, 1903, p. 187.
[2] Comptes-rendus Acad. Sc., June 22, 1903, p. 1529.
[3] Ibid., October 19, 1903, p. 624.

phological characteristics of these organisms as shown in stained preparations, even when these are made from the same kind of animals, as, for instance, the white mouse, are such as to leave little doubt that they are distinct species.

A further and perhaps even more conclusive method of differentiation is to be sought for in the cultural characteristics of the trypanosomes found in these diseases. Thus it has been shown that in artificial culture the *Trypanosoma lewisi* is wholly unlike *Trypanosoma brucei*. If, therefore, surra and nagana are one and the same disease, as has been asserted by some observers, it is evident that the cultures obtained from these sources must be identical in every respect. On the other hand, if such cultures show distinct differences it can mean only one thing, and that is that the organisms and hence the diseases are wholly unlike.

In order to approach this question it was necessary to secure living surra trypanosomes. These could not be obtained by direct shipment of the infected blood, for, like those of nagana, they die out within a few days after the removal of the blood from the body. Accordingly another procedure was resorted to. One of us (Mr. Hare) before leaving for the Philippine Islands last summer was requested to inoculate blood-agar tubes with surra blood and ship these to Ann Arbor. Inasmuch as this medium was the same as that employed for the cultivation of *Trypanosoma lewisi*[1] and of *Trypanosoma brucei*,[2] it was assumed that out of a series of tubes thus sent perhaps one or more would reach their destination with living and even multiplying trypanosomes.

The first shipment was negative, but the second, consisting of three tubes, was even better than had been anticipated. These tubes of blood agar were inoculated on January 1st with the blood of an American cow suffering with surra. The inoculated tubes were kept for three days in cold storage, after which they were shipped to Ann Arbor, where they arrived on February 8th, or thirty-eight days later.[3]

One of the tubes was fairly rich in motile trypanosomes, the

[1] Contributions to Medical Research dedicated to Victor Clarence Vaughan, Ann Arbor, Mich., 1903, George Wahr, p. 563.

[2] Journal of the American Medical Association, November 21, 1903; Journal of Infectious Diseases, 1904, vol. i. p. 1.

[3] Since writing the above we received a third shipment of three tubes of inoculated blood agar. The medium used was 3 to 2, 1 to 1, and 1 to 2. The tubes were thirty-nine days en route, and on their arrival showed no trypanosomes.

second was even better, while in the third they were very abundant. The appearance and size of the organisms were such as to leave no doubt but that they had developed en route, and that the material received was in reality a culture of the Philippine surra trypanosome.[1]

It was evident at the outstart that the trypanosomes in this culture were entirely different from *Trypanosoma lewisi* and *Trypanosoma brucei*. Thus there was an entire absence of the groups or rosettes which are so characteristic of the culture of these two organisms. The trypanosomes were all single and actively motile. They travelled as readily with the flagellum in the rear as with it in front. Another striking feature was the size of the cell and especially the length of the flagellum. An even more marked characteristic was the presence and peculiar arrangement of granules within the cells and the distinct yellowish or greenish color of the granules and of the contents.

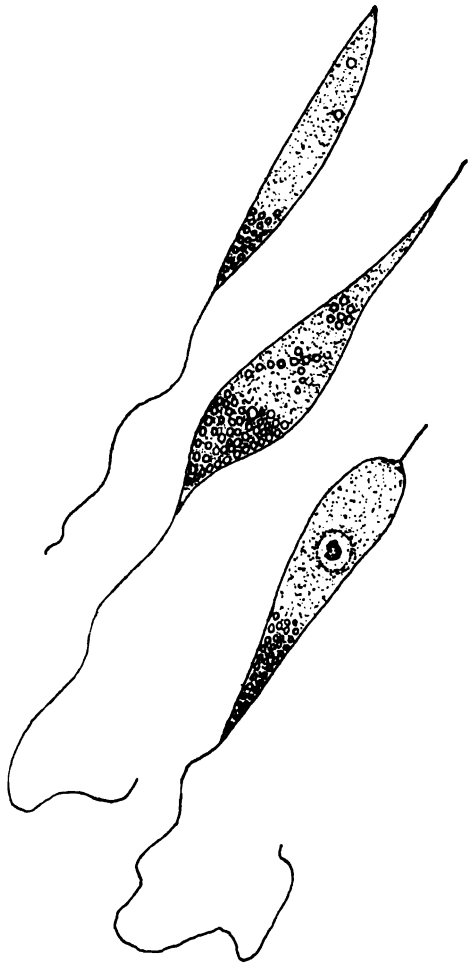
The contents of the cell in the case of the cultivated *Trypanosoma lewisi* are colorless and almost homogeneous; at most but a few very minute granules can be made out. On the other hand, *Trypanosoma brucei* presents a striking contrast, since, in cultures, it shows one or two very large, bright and highly refracting globules in the otherwise homogeneous, colorless cell. The new trypanosome, however, showed large numbers of small granules or globules which varied from 0.3 to 0.5 micron in diameter. These globules, as well as the contents of the cell, possessed a decided yellowish or greenish color, an appearance quite unlike that of either of the other two trypanosomes. These globules were usually massed in the anterior third of the cell—that is, at the base of the flagellum—and only a few isolated granules were scattered through the remainder of the organism. In the divisional forms the granules were arranged in two parallel rows, thus imparting a very characteristic appearance to the organism. Only exceptionally were individuals to be found

[1] Since the publication of the work on the cultivation of *Tr. lewisi*, Laveran and Mesnil have endeavored to apply the same method to the trypanosomes of surra and caderas. Under date of December 18th, Dr. Mesnil wrote to one of us (Novy) that they had obtained with surra encouraging results quite analogous to those obtained by us with *Tr. brucei*. Just how far they were successful in their experiments we are unable to state, since they have published nothing on the subject.

It may be stated in this connection that the culture of *Tr. lewisi* begun on May 16, 1902, and grown at room temperature is now in its twenty-sixth generation. The other strain which we reported on, begun December 4, 1902, and grown at 34° to 37° C., is at present in its sixty-seventh generation. The culture A of *Tr. brucei*, which was started on August 27, 1903, is now in its twenty-seventh generation.

which contained one or several large globules, 1 or 2 microns in diameter, instead of the arrangement described. The latter may perhaps be looked upon as dying or degenerating forms.

FIG. 1.

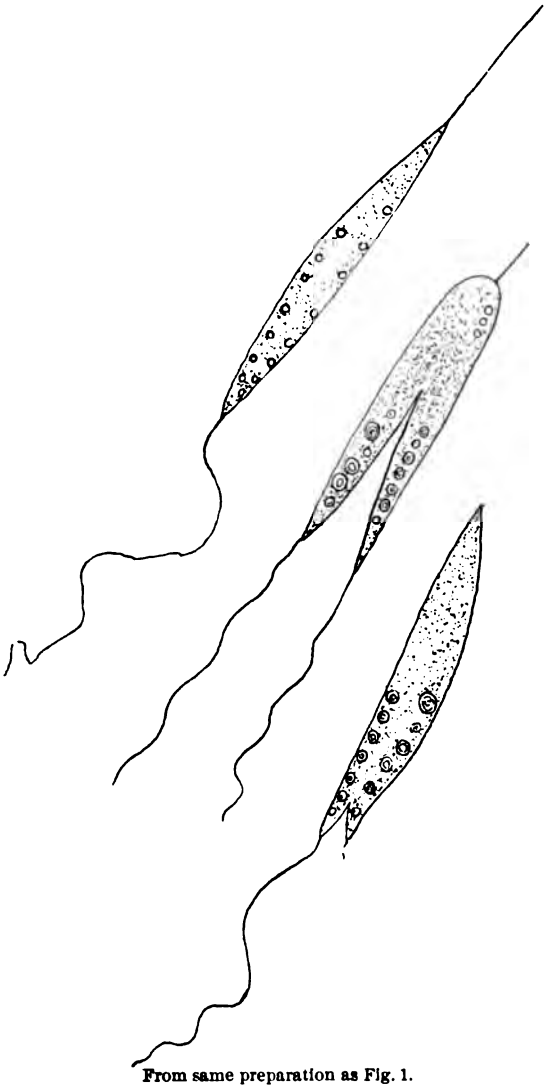


Philippine surra trypanosomes, from thirty-eight day culture and drawn from a living preparation. Magnification, approximately 3000 ×.

The trypanosomes thus received were apparently in perfect condition and had all the appearance of a healthy culture. As already stated, they were always single and were extremely motile, travers-

ing the field of the microscope at great speed. When the flagellum was in front the side-to-side lashing was marked, whereas, when it

FIG. 2.



From same preparation as Fig. 1.

was in the rear, the cell travelled with a rapid, straight, dart-like motion. The slender body terminated at one end in a delicate

flagellum, which was usually as long and often even longer than the cell itself. Thus the body of one large individual measured 21 microns, while the flagellum was 28 microns in length.

The posterior end, especially when blunt, showed a rod-like tip or stylet, which varied from 2 to 4 or even 6 microns in length. (See Figs. 1 and 2.) The undulating membrane was not recognizable in the living organism.

The total length of the trypanosomes, as might be expected in a culture, varied considerably. The exceptionally long forms measured from 40 to 50 microns. Most of the individuals ranged from 25 to 35 microns. The width of the cells varied from 1.5 to 2.5 microns.

As the cultures aged, pear-shaped or spherical, highly granular involution forms appeared. In the former type, measuring about 3 by 5 microns, the end was often provided with a flagellum 10 to 15 microns long, which still showed a slow, lashing movement, though the cell itself was motionless. The spherical forms varied from 4 to 9 microns in diameter, were very granular, and often showed a remnant of the flagellum as a short, stiff, motionless whip. These involution forms, as in the case of *Trypanosoma lewisi* and *Trypanosoma brucei*, eventually gathered into large groups or masses which at times filled the field of an oil-immersion lens. Later on, perhaps as a result of autolysis, the round bodies broke up into masses of very minute granules.

The tube which contained the fewest organisms was the first to lose them. No living forms were found in it on the forty-eighth day. It is noteworthy, however, that in the richest tube the trypanosomes were still alive, though very few, on the sixty-fifth day. Under an ordinary cover-glass on a slide the organisms remained alive for many hours. In one instance, where complete desiccation was prevented by the formation of a dried ring, a few were still alive after fifty-two hours.

Immediately upon the receipt of the culture tubes several attempts were made to inoculate animals and to obtain a second generation. It was particularly desirable to secure an infection of animals, for in that event a constant supply of surra material could be maintained, and this would serve as a point of departure for further cultivation experiments in case the original material failed to yield subcultures. It may be said in advance that all these attempts at inoculating animals and obtaining subcultures proved fruitless.

Only a brief mention need be given, therefore, of these experiments.

A portion of the fluid from the thirty-eighth-day culture, richest in trypanosomes, was injected into the peritoneal cavity of two white mice, two white rats and a guinea-pig. The mice and rats each received two drops, while the guinea-pig received a quarter of a cubic centimeter of the liquid. The blood of these animals was examined every day or two for a month for the presence of trypanosomes, but none could be found. The mice and rats remained alive and in perfect condition. The guinea-pig died on the thirtieth day, but at no time did it show any parasites in its blood. The heart blood, drawn immediately after death, gave a culture of a very minute bacillus. In order to detect, if possible, any trypanosomes that might be present, portions of this blood were injected into each of two white rats and two guinea-pigs. Both rats died on the sixth day and one of the guinea-pigs died on the seventh day. Notwithstanding daily examinations trypanosomes could not be detected in the blood of these animals. The heart blood of these animals gave a culture of the small bacillus mentioned. The second guinea-pig remained alive and in good condition for nearly two months. It was evident from these inoculations that the first guinea-pig did not die of trypanosomiasis, but of an infection following upon the repeated examinations of its blood.

On February 18th, when it was evident that the above animals would probably fail to develop a trypanosome infection, possibly because the dose employed was too small, the entire contents of one of the tubes was inserted under the skin of a guinea-pig. This inoculation likewise failed to infect.

The failure to produce infection in animals by the inoculation of the thirty-eighth and forty-eighth-day culture of this trypanosome corresponds to the observations which have been made on *Trypanosome brucei*.[1] In the latter case first generations, twenty-nine and thirty-eight days old, respectively, failed to infect mice. It would seem as if the unfavorable conditions under which the first generation is developing results in an early and complete loss of virulence. Since in the second and subsequent generations of *Trypanosoma brucei* this virulence is largely restored, it was hoped that a like result would be met with in the subcultures of this try-

[1] Journal of Infectious Diseases, 1904, vol. i. p. 21.

panosome. This hope, however, was not realized, for notwithstanding numerous and varied attempts to secure such subcultures all efforts failed.

Between February 8th and March 1st seven attempts were made to secure a second generation. In all thirty-eight flasks and tubes of blood agar were inoculated. The blood-agar mixture varied from 1:1 to 2:1; the proportion of beef and water from which the meat extract was prepared for the nutrient agar varied from 1:1 to 1:8; and again the amount of sodium carbonate used in the preparation of the agar varied from nothing to 20 c.c. of the normal solution per liter. The nutrient agar contained, as a rule, 2 per cent. of agar and a like amount of peptone, together with half per cent. of salt. The inoculated flasks were kept at 5°, 15°, 25° and 34°, but without avail. At no time was there any indication of a second generation.

It will be seen from the foregoing that the first generation in artificial culture of the trypanosome of the Philippine surra was incapable of developing either in the animal body or in the culture media. The failure to obtain a second generation in this case must be ascribed to the fact that the culture was thirty-eight days old when received, and that the trypanosomes, notwithstanding their apparently excellent condition, were too enfeebled to reproduce. An exactly similar behavior, it should be noted, has been observed in connection with *Trypanosoma brucei*, where the first generation, twenty-nine days old, failed to infect animals or to yield subcultures on blood-agar media. It is possible, however, to obtain cultures from a first generation of the nagana trypanosome at a much later date than that just given, provided the amount of salts and other extractives in the medium employed are decreased. Under such special conditions it was possible to obtain a subculture from a first generation of *Trypanosoma brucei* when fifty-two days old. Without doubt, under like conditions, a similar result can be obtained with the Philippine and other trypanosomes. Obviously no difficulty should be experienced in securing transplants from a first generation if such attempts are made on about the third to the fourth week.

The foregoing observations, although they are by no means as complete as we would like them to be, are nevertheless quite sufficient to show that the trypanosome of the Philippine surra is distinct from that of the South African nagana. It seems to us that there cannot be any question on this point.

The studies of the past ten years have shown that there are not less than six very important trypanosomatic diseases in Africa. These diseases, excluding those of birds, amphibians, and fish, are: nagana, dourine, galziekte, zousfana, Gambian horse disease and human trypanosomiasis. The latter designation includes the Gambian or trypanosomatic fever of Dutton and Forde and the so-called sleeping sickness, which really are but different stages of infection due to *Trypanosoma gambiense*, a fact which has been established by Laveran and other workers.

In Asia, on the other hand, ever since the work of Evans in 1880, only one trypanosomatic disease has been recognized, namely, surra. This fact serves to indicate the need of a careful comparative study of this disease as met with in different parts of Asia and in the islands of the Pacific. It is more than probable that the term surra will be found to cover several distinct infections. On this point we have one observation to offer which is very suggestive and which obviously will require further study to ensure its correctness.

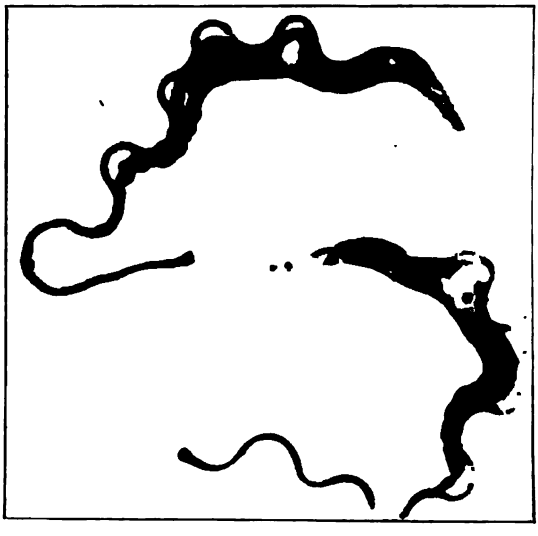
Some time ago we obtained through the courtesy of Dr. Mesnil, of the Pasteur Institute, a number of preparations made from the heart blood of a mouse infected with the surra trypanosome brought from the Island of Mauritius. A comparison of the preparations having this origin with one from the Philippine Islands shows that the two organisms are quite unlike. In making this comparison the large Zeiss microphotographic apparatus was used to advantage. The individual trypanosomes were studied upon the ground-glass plate at a suitable magnification, such as 3000 diameters. Microphotographs taken at this magnification were very useful for measurements and other studies. The length of a trypanosome was ascertained by tracing a string along the border opposite the undulating membrane from end to end, and then laying this off on a ruler. At a magnification of 3000 diameters a micron corresponds to 3 mm. It is consequently possible to measure the length of a wavy object in this way more accurately than with an eye-piece micrometer.

The total length of the Mauritian trypanosome was on an average 33 microns; the free flagellum was 13 microns, while the width, not counting the wavy expansion of the undulating membrane, was about 1.5 to 1.7 microns. The total length of the Philippine trypanosome was from 22 to 25 microns; that of the free flagellum was

8 to 10 microns and the width was from 0.3 to 1.7 microns. A marked difference therefore exists in the lengths of the individuals and of their free flagella.

An even more marked difference can be seen in the distance of the centrosome from the end. Thus, in the Mauritian trypanosome this distance measures 3.3 to 4 microns, while in that from the Philippines it is only 1 to 1.6 microns. In the latter case the centrosomes were nearly all elongated preparatory to division.

FIG. 3.



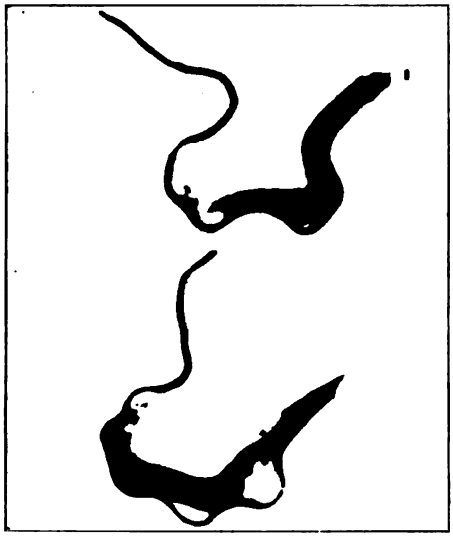
Photograph of trypanosome of Mauritian surra, from blood of mouse. Preparation stained by Romanowsky-Nocht method. Magnification, 3000 ×.

The undulating membrane was more developed in the Mauritian trypanosome than in that of the Philippines. In the former it shows four distinct waves which are very suggestive of *Trypanosoma brucei*. In the Philippine trypanosome two of three less-marked waves represent the undulating membrane.

Another point to which attention may be called is the presence of heavily stained granules in the anterior half of the Mauritian trypanosome. The posterior half of the body is quite free from these bodies. On the other hand, the Philippine trypanosome stained heavily in the posterior two-thirds.

Obviously too much importance must not be attached to comparisons made under these conditions, especially since the Philippine preparation was stained before it was sent. The observations given seem to indicate that they are two distinct organisms. The proof of this view can be supplied in part by the study of preparations made from the same kind of animal, such as the white mouse or white rat, obtained from different regions where surra is said to exist. A positive demonstration, however, can be made either by the immunity experiment such as has been done by Laveran and

FIG. 4.



Photograph of trypanosome of Philippine surra from blood preparation. Magnification, 3000 ×.

Mesnil in their studies upon nagana, caderas, and the Mauritian surra, or by the cultural method which we have employed.

Summing up the main facts presented in this paper we may say that:

1. The trypanosome present in the Philippine surra can be cultivated artificially.

2. Attenuated cultures of this organism can be obtained as in the case of *Trypanosoma brucei*.

3. This trypanosome is differentiated by its cultural characteristics from *Trypanosoma lewisi* and from *Trypanosoma brucei*.

4. The Philippine surra is therefore a distinct disease, different from nagana, and this observation confirms the work of Laveran and Mesnil on the non-identity of nagana and the surra of Mauritius.

5. The morphologic differences between the Mauritian and Philippine trypanosomes suggest the probability that these organisms are distinct species, and hence that the term "surra" covers a group of closely allied diseases.

A CLINICAL REPORT OF NINE CASES OF DIABETES INSIPIDUS.

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I find that the subject of diabetes insipidus has never been presented before this Association. This circumstance, together with the fact that I am privileged to report the clinical records of nine cases of this disease, a number of which show features of special interest, is my justification for bringing up the subject for consideration to-day.

Three names are intimately associated with the problem of differentiating the various forms of polyuria. Thomas Willis,[1] in 1674, first recognized a distinction between a saccharine and a non-saccharine diabetes, by discovering the fact that in certain cases of polyuria the urine had a sweet taste. Johann Peter Frank,[2] in 1794, first gave us a definition for diabetes insipidus when he described it as a long-continued, abnormally increased secretion of non-saccharin urine which is not caused by a diseased condition of the kidneys. He distinguished two forms of diabetes, a *diabetes insipidus* or *spurious* and a *diabetes mellitus* or *verus*. Robert Willis,[3] in 1838, proposed a classification of cases of diabetes insipidus according to the amount of solids in the urine. He was led to believe that there were three fairly distinct groups —the hydruria, azoturia and anazoturia cases. This classification is now practically abandoned, and Senator holds that the various forms do not represent independent diseased processes, but merely various stages of one and the same affection, the amount of solids excreted being dependent on the condition of the digestive tract.

EXPERIMENTAL POLYURIA. Before proceeding to a consideration of the disease it may contribute to our understanding of the manner in which certain pathologic lesions, occasionally found in this affection, cause the polyuria, by briefly reviewing the work that has been done on experimental polyuria in animals.

In 1849 Claude Bernard,[4] in experimenting on animals, found that injury of a point in the floor of the fourth ventricle between the centers of the pneumogastric and auditory nerves caused transitory glycosuria—the so-called diabetic center. What is more important in the present consideration, however, is the fact that he found that injury of a point a little above this produced simple polyuria. This observation threw much new light on the etiology of many cases of diabetes insipidus. Claude Bernard studied the physiology of urinary secretion farther, and his results may be summarized as follows:

1. Stimulation of the vagus in dogs has no effect on the color of the renal veins or on the secretion of urine. In rabbits, on the other hand, three notable results follow: a dilatation and increased redness of the renal veins and an increase in the urinary secretion.

2. Section of the greater splanchnic nerve causes, in dogs, an immediate increase in the amount of urine secreted. This increased functional activity can be stopped by stimulating the peripheral end of the cut splanchnic with the galvanic current. In rabbits, section of the greater splanchnic causes the renal veins to contract and assume a darker red color. Stimulation of the peripheral end of the cut splanchnic nerve had no result.

3. In rabbits at least, section of one of the greater splanchnics influence only one kidney, viz., the one on the same side, whereas each of the vagi was found to influence both kidneys.

4. The splanchnic and vagi are antagonistic in their action on the renal vessels in rabbits.

Claude Bernard's conclusions, although not confirmed in every detail by subsequent experiments, really formed the foundation for all future work. The researches of Eckhard,[5] of Giessen, for the most part confirmatory, while demonstrating some errors, have added much to our knowledge concerning the effects of nervous influences on urinary secretion, and have filled up many previously

existing gaps. His results embrace practically all that we know at present on this point, and may be summarized as follows:

1. Wounds of the floor of the fourth ventricle frequently produce polyuria, but the lesions do not always involve the point already demonstrated by Bernard. In rabbits, at least, there is no definite point in the floor of the fourth ventricle, injury of which will constantly produce a pure "hydruria."

2. The vagus has absolutely no influence on the secretion of urine in dogs or rabbits.

3. Cutting of the greater splanchnic nerve in dogs produces an immediate increase in the urinary secretion, the amount being about four times that normally eliminated. Stimulation of the peripheral end of the cut splanchnic stops the increased elimination. The greater splanchnic is therefore the vasomotor and special secretory nerve of the kidneys in dogs. In rabbits the splanchnics have absolutely no influence on the urine secretion.

4. In dogs each splanchnic supplies branches to only one kidney, viz., to the one on the corresponding side, and, after cutting the nerve, more urine is secreted only by that kidney which is on the same side as the cut nerve.

5. All other macroscopically recognizable sympathetic nerves going to the kidney, as well as their anastomoses with the phrenic and vagus nerves, have no influence on the urine secretion.

6. Only the highest thoracic sympathetic ganglion and those fine nerve fibrils which pass in the thoracic cavity to the aorta and surround it, as well as other arteries, including those of the kidney, as a fine network, appear to influence the urine elimination. These nerves, however, are so fine that their influence cannot be determined by experimenting upon them directly, so that conclusions regarding their action can only be obtained by eliminating their function through section of the spinal cord.

7. Section of the spinal cord at the level of the sixth or seventh cervical vertebra, as well as at higher levels, produce without exception an immediate and persistent suppression of the urine. Sections below this level give less certain and less prompt results, whereas sections of the cord below the twelfth dorsal vertebra have practically no effect whatever.

8. The diminished urine secretion following section of the cord is not the result of diminished blood pressure.

9. From the results of section of the cord at the above indicated level, it is apparent that the center regulating the urine secretion is above this point; from the effect of medullary puncture it is quite certain that the center is in the medulla or higher up.

10. It may be concluded, then, that the nerve fibers supplying the kidneys pass from the medulla in the spinal cord to the level of the sixth or seventh cervical vertebra, where they leave the cord in the uppermost thoracic nerves, whence they pass along the walls of the aorta and renal arteries to the kidneys.

11. There are a few poisons which produce a polyuria similar to that following Bernard's medullary puncture; among such poisons are curare and carbon monoxid.

12. In addition to Bernard's center there are other areas of the brain, injury of which produces a temporary polyuria. Eckhard demonstrated that temporary polyuria followed

(*a*) After mechanical injury of the vermiform process of the middle lobe of the cerebellum, in which experiment, as he emphasizes, the blood pressure remains uninfluenced. The polyuria is most readily produced by injury of the most posterior of the convolutions of the middle lobe of the cerebellum seen from above. To this convolution Eckhard suggested the name "lobus hydruricus et diabeticus," "diabeticus" because the polyuria was frequently accompanied by glycosuria.

(*b*) After chemical irritation of the same point with iron chlorid, acetic acid, caustic potash or silver nitrate.

(*c*) After electric irritation of the same.

(*d*) After injury of the posterior lobe of the rabbit's brain (the lobe which lies in the concavity of the temporal bone), the lesion requiring to be comparatively deep, however.

The results under Section 12 were obtained only with rabbits, the experiments being entirely negative with dogs.

Kahler,[6] later on, in experimenting on rabbits, was able to produce a permanent polyuria in animals closely resembling diabetes insipidus in man. By injecting minute quantities of concentrated silver nitrate solution into various parts of the brain he could

cause a polyuria accompanied by polydipsia, both lasting several weeks. Microscopic examination of the involved brain areas were afterward made in order to determine exactly the localization and extent of the lesion. Kahler's results in brief were as follows:

1. One can produce a permanent polyuria in rabbits by destruction of minute areas of the cerebellum and medulla oblongata.

2. Whereas injury of the middle lobe of the cerebellum produces a more or less temporary polyuria, wounds of the medulla oblongata, on the other hand, are followed by a permanent polyuria.

3. The corpus trapezoides of the pons and the lateral part of the exposed portion of the medulla oblongata are the areas injury of which is most likely to produce a permanent polyuria.

4. Destruction of the inner part of the cerebellum with Dieter's nucleus and its caudal processes causes practically always a permanent polyuria.

5. Experimentally produced permanent polyuria must be regarded as an irritation phenomenon.

6. The portions of the rabbit's brain designated in Section 3 correspond in the human brain with the area of the pons where the sixth and seventh cranial nerves make their exit from the brain.

One would look for a persistent polyuria, then, in human beings when the lateral portion of the distal part of the pons and the proximal portion of the medulla are involved in some lesion.

From the experimental work of these various observers it would appear that a polyuria in rabbits and dogs can be produced by injuries in the floor of the fourth ventricle, by lesions in different parts of the middle lobe of the cerebellum and by injuries to the posterior portion of the pons. From analogy we would rather expect to find polyuria in man if brain lesions in these situations existed. One can easily see how tumors situated toward the posterior part of the base of the brain, as well as basilar meningitis, of syphilitic or other origin, could possibly produce a permanent polyuria.

There are still many points in dispute concerning the method of the production of polyuria in brain lesions. Is the polyuria the result of the action on special secretory nerves in the kidney? or is it a question of blood-pressure effect? Eckhard believed

that he had proved the existence of special secretory nerves, but all the leading modern physiologists deny the existence of such nerves, and believe that the polyuria is a question of increased blood pressure. Eckhard claimed, however, that in his experiments the blood pressure is not increased. Whereas, the balance of opinion is in favor of the polyuria being due to increased blood pressure in the renal vessels, the question is still a more or less open one.

The possible effect on the urinary secretion of remote lesions of the nervous system was clearly stated by Ralfe[7] as follows: "It is interesting to trace the course of the nerves forming the renal plexus, as irritation from eccentric or distant sources may play a part in inhibiting the renal nerves. Thus the nerves forming the renal plexus are derived chiefly from the solar plexus; it is probable that branches of these nerves enter the kidney by way of the renal plexus. Splanchnics also send branches direct to the renal plexus, and the left vagus sends some fibres to the left kidney. They contain medullated and non-medullated fibres; and Krause has traced the latter as far as the apices of the papillæ. Their mode of termination is unknown. Physiologically, vasoconstrictor, vasodilator and sensory nerves have been ascertained. The connection through the vagus brings us into range with the medulla oblongata and with many organs susceptible of tubercular or syphilitic growths, or of sudden shock, such as chill. The solar plexus may propagate the effect of abdominal new-growths or aneurysms."

Incidence. Diabetes insipidus belongs to the rarer of the medical diseases. Of the 9 cases here reported 7 were treated at the Johns Hopkins Hospital—6 in Dr. Osler's medical wards and 1 in the medical department of the dispensary. The other 2 were private patients. One of these, Case I., was a patient of Dr. Thayer, who asked me to look after the child during an acute febrile upset in his absence from the city, and to whom I am indebted for being able to include the case in the present series.

These 7 cases comprise all the cases of diabetes insipidus that have been treated in all the departments of the hospital, both in the wards and in the dispensary, since it was opened on May 15,

1889. In other words, there were 7 cases out of a total of 403,535 patients treated in the hospital and dispensary up to May 1, 1904, making 0.001 per cent. During this time there were 17,042 admissions to the medical wards, 6 of which were diabetes insipidus cases, or 0.03 per cent. of the medical cases. Among 113,600 patients treated at the Charité, Berlin, from 1877 to 1896, there were 55 cases, or 0.048 per cent. Eichorst observed 7 cases, or 0.02 per cent., among a total of 35,942 patients at the Zürich Hospital.

Clinical Classification of Diabetes Insipidus. It seems best at this point, before taking up the etiology, to refer to the clinical classification. Two forms are generally recognized according to the etiology:

1. *Primary or Idiopathic Cases.* This group includes the cases in which there is no evident organic basis for the disease.

2. *Secondary or Symptomatic Cases.* These include the cases in which there is evidence of organic disease either in the brain or elsewhere, the lesion being considered the cause of the diabetic symptoms. Gerhardt includes in this group also those instances where the disease occurs in psychoses and in hysteria or neurasthenia. He states that it is very difficult to draw a definite line between certain cases in the two groups.

In the series here reported 4 belonged to the idiopathic and 5 to the secondary or symptomatic group. In 4 of these 5 cases syphilis was the probable cause of the disease, and in all of them there were very marked evidences of cerebral lues.

Stoermer,[8] in his monograph on the disease, gives the following useful classification:

1. Diseases of the central and symptomatic nervous systems where actual anatomic changes occur.

This group includes the cases occurring—

(*a*) After trauma.

(*b*) After diseases of the brain and spinal cord, such as brain tumors, apoplexy, cerebral syphilis, hydrocephalus, general paresis; also after bulbar disease and diffuse diseases of the cord.

(*c*) After diseases of the cranial bones and vertebræ and of the meninges.

(*d*) After diseases of individual nerves, such as result from the pressure of an aneurysm and disease of the middle ear.

(*e*) After disease of the sympathetic nerves and ganglia, including the cases occurring after intestinal disease and after exophthalmic goiter.

2. Diseases of the cerebrospinal and sympathetic nervous system without appreciable anatomic changes. This group includes the cases following:

(*a*) Psychical derangements.

(*b*) Acute and chronic alcoholism.

(*c*) Epilepsy and hysteria.

(*d*) Inherited and psychic neuropathic characteristics.

3. Injury to general health, as from excessive bodily and mental activity, effect of intense heat, poor nourishment and particularly catching cold.

4. Infectious diseases—diphtheria, measles, scarlet fever, intermittent, typhus and typhoid fever.

5. Cases without any discoverable cause whatever.

Etiology. The disease is commonest in comparatively young persons. Of the 85 cases analyzed by Strauss[9] the largest number (36) occurred between ten and twenty-five years. In the statistics collected by Roberts, van der Heijden and Stoermer the largest number of cases occurred between twenty and thirty years of age. Gerhardt,[10] in his excellent monograph, states that more than one-half of all the cases occur between the tenth and fortieth years. The ages of the patients in the present series were as follows: thirteen, twenty-five, thirty, thirty-two, thirty-four, thirty-five, thirty-six, forty-four and fifty-seven years. The largest number (5) occurred between thirty and forty years of age; 7 of the 9 cases were males. Trousseau noted that it was not unusual to find that the parents of patients suffering from diabetes insipidus were either glycosuric or albuminuric. Ralfe emphasized the frequency with which a history of tuberculosis, syphilis and gout was obtained in one or both parents.

Case I. well illustrates the point brought out by Ralfe concerning tuberculosis in the ancestors. Although the patient had an apical pleurisy, suggesting a tuberculous infection, the case has

been placed in the idiopathic group, there being no cerebral symptoms. Ralfe also believed that malnutrition was a very important predisposing factor in the etiology of the disease in children.

The following case is a private patient of Dr. W. S. Thayer, who asked me to look after her for a few days, in December, 1903, during his absence from the city. Dr. Thayer has kindly permitted me to report the case, and I am indebted to him for the following history and notes:

CASE I.—*Diabetes insipidus in a girl aged thirteen years and belonging to the idiopathic group; very marked history of pulmonary tuberculosis on the father's side of the family; an apical pleurisy of brief duration; no evidence of meningeal symptoms.*

M. D., white, female, school-girl, aged thirteen years, first came under observation on October 1, 1903, complaining of increased thirst and frequency of micturition.

The child's paternal grandfather, grandmother, two paternal aunts and an uncle all died of pulmonary tuberculosis. Her maternal grandfather died three years ago of pneumonia. The patient is the only child, and there is no history of any diabetes in the family.

She had always been a fairly healthy child. Six years ago a lump appeared on the left leg. It softened, but did not discharge. For a number of winters she was subject to attacks of bronchitis. From May to about the middle of August, 1902, she had a very severe attack of whooping-cough.

The present illness began in January, 1903, when her parents noticed that the child began to drink large quantities of water, accompanied by a corresponding increase in the flow of urine. Her mother states that she at first would have to leave a glass of water on the mantel-piece to quench the child's thirst; then two glasses; then three and finally a pitcher of water. The appetite is variable; at times it is much increased.

In April, 1903, she consulted a physician who made a diagnosis of diabetes mellitus. She was placed on a very much restricted carbohydrate diet. Her weight one year ago was 108 and now it is 95½ pounds.

Physical Examination. Tall child; rather thin; face rather pale, but lips and mucous membranes of a good color. Tongue not dry. Radial arteries soft. Pulse 80 to the minute at the beginning of the examination. Blood pressure 130 mm. Hg (Riva Rocci instrument).

The thorax is a little long; costal angle just under 90 degrees; expansion equal. The lungs are clear throughout on percussion and auscultation.

The point of maximum cardiac impulse is visible and palpable in the third space about 7 cm. from the median line. First sound is a little prolonged,

but clear. The second sound is reduplicated at the apex; rather a long period between its reduplications. This is lost inside of the parasternal line; not heard at the base. No reduplications of the second sound at the base. Soft systolic murmur at the base on both sides, over the manubrium and in the carotids. At times, particularly just outside the apex, the prolongation of the first is long enough to be regarded as a real murmur. In the erect posture the sounds are just the same. Action is perfectly regular.

What is apparently the bladder can be felt a little to the right rather than to the left of the median line, extending about one-third of the way to the umbilicus. Liver is not enlarged. Right kidney is just palpable. Spleen is not palpable.

Two specimens of urine, a night and a morning specimen, were examined by Dr. Hamman. They showed respectively specific gravities of 1001 and 1002. There was a very faint trace of albumin in both of them; no sugar and no casts in the sediment.

The child, on the basis of this analysis, was placed on a fuller and more nutritious diet and given a simple bitter tonic.

On December 7, 1903, Dr. Thayer examined the eye-grounds. The disks were perfectly clear and the fundi showed no abnormalities.

During the last week in December, 1903, I saw her for what the family called a "cold." She had considerable cough and a good deal of pain referred to the left shoulder and increased by coughing and deep breathing. For two or three days there was considerable fever, the temperature rising at 9 P.M. on December 27 to 104°. Examination of the lungs showed no impairment of the percussion note, but slight tubular modification of the breath sounds over the left supraspinous fossa, where a superficial leathery friction rub was heard on December 28. The sputum, which was slightly mucopurulent, showed no tubercle bacilli. The patient was quite well of the pulmonary symptoms in about ten days.

Urine Examinations. The urine has been examined once or twice a month up to the present time. The twenty-four hour amounts when measured have been as follows: 2900, 5200, 4200, 3000, 4200, 3200, 3700 and 3400 c.c. On April 10, 1904, the last examination was made. The specific gravity has never been above 1003.5. The color has always been very pale, taking on a slight yellow tint at times. Albumin has been present in very minute traces at times. Sugar has been persistently absent and casts have never been found. The urea excretion has ranged from 9 to 19 grams in the twenty-four hours.

Treatment. When it was found that the case was not one of diabetes mellitus and the child was placed on a liberal diet her weight steadily increased. For several months she was periodically placed on 8 minims of tincture of ergot three times daily, with some apparent benefit. At intervals she has also had courses of tincture of belladonna in 12-minim doses three times daily, but without any marked diminution in the urine.

The child's general condition at present is very good. She seems quite well with the exception of a slight cough. The lungs show no evidences of disease at present. Her weight now is 107 pounds.

Heredity is a very important predisposing factor in a certain percentage of cases. Without multiplying examples it is sufficient to say that the most remarkable instance was in the family reported by A. Weil.[11] Of 91 members of four generations 23 had persistent polyuria without any deterioration of health, namely, the great-grandfather, 3 children, 7 grandchildren and 12 great-grandchildren. Of the 22 affected descendants there were 11 males and 11 females.

Traumatism to the nervous system is not an infrequent cause. According to Stoermer, 30 per cent. of all cases are traceable to injuries of the brain alone. Trauma to the soft parts and bones of the body does not produce diabetes insipidus. The only authentic exception to this statement is a case reported by Nothnagel, in which diabetes insipidus followed a kick on the abdomen. The essential factor in these trauma cases is, as we would expect, an injury to the brain substance itself. The disease does not appear to be confined to or to be commoner after injury to any special part of the brain. The polyuria is believed to be due to the effects of the concussion the brain sustains.

The disease not infrequently follows a *cerebral hemorrhage*. In 1865 Leyden[12] reported such a case, and Ollivier at a subsequent date drew attention to their frequency.

Cerebral tumors rank at the head of the list of gross brain lesions in the frequency with which they are followed by diabetes insipidus. The nature of the tumor appears to be a minor factor. It may be a gumma, a malignant growth or a tuberculous focus. The situation is of greater importance. The disease occurs most frequently in association with tumors which involve the floor of the fourth ventricle or which are situated in the immediate vicinity. On the other hand, tumors frequently occur in this situation without producing a diabetes insipidus.

Polyuria and polydipsia have long been described as symptoms of *cerebral syphilis*. Fournier reported 6 cases in which these symptoms were present in association with various cerebral mani-

festations of the disease. Lancereaux, Oppenheim and others have also noted the association. The lesion usually producing the polyuria is a basilar syphilitic meningitis. This was the form of lues in Buttersack's case, in which the disease was localized mainly in the interpeduncular space. Polyuria was the initial symptom in his patient. Nonne[13] states that it is not necessary, as was formerly held, that the lesion should involve the medulla oblongata or its vicinity. He asserts that all we can say is that polyuria and polydipsia are most liable to occur in syphilitic brain lesions which manifest themselves in the form of a diffuse basilar meningitis. Many of the cases of diabetes insipidus due to syphilitic basilar meningitis have been associated with bilateral hemianopsia.

Oppenheim considers an "oscillating" form of hemianopsia or an "hemianopsia bitemporalis fugax" as being practically pathognomonic of basilar cerebral lues. He has reported 3 such cases, in one of which polyuria and polydipsia were associated. In this case, besides the hemianopsia, there were other evidences of basilar meningitis in the form of a double oculomotor paralysis and anosmia. Spanbock and Steinhaus[14] state that in 50 cases of temporal hemianopsia reported in the literature there was polyuria in eleven instances; 2 of our 5 cases in which cerebral lues was believed to be the cause gave a history of hemianopsia, which, however, did not exist during the period of observation.

We have been particularly impressed in the consideration of the etiology of the disease in the present series with the frequency of syphilis as an etiologic factor; 4 of the 9 cases (Cases II., III., IV., V.) were undoubtedly due to this cause. Two others (Cases VI. and IX., particularly Case IX.) were probably also luetic in origin, but, as positive evidence was lacking, it was deemed better to be conservative and place them with the so-called idiopathic group. All the cases had very remarkable cerebral symptoms, as the histories show.

The following case was undoubtedly one of cerebral lues. The history of his attacks of transitory hemianopsia suggests strongly that there was a basilar luetic involvement of the brain, probably a gummatous meningitis:

CASE II. (*Gen. Hosp., No.* 38162). *Diabetes insipidus due to cerebral syphilis; dragging of the right leg and severe cerebral symptoms, with unconsciousness of a week's duration preceded the onset of thirst and polyuria; recurring transitory attacks of hemianopsia an early symptom of the cerebral disease; urine in excess of fluids; day urine exceeded the night urine; knee-jerks exaggerated.*

L. R, male, married, aged thirty-five years, a business man from Ohio, consulted Dr. Osler on February 7, 1902, complaining of great thirst, and was sent into the Johns Hopkins Hospital, on March 10, for observation.

Family history excellent. Thirteen years ago he contracted syphilis, but was well and thoroughly treated. Married nine years ago; has healthy children. Three years ago he had an attack of what his doctors said was cerebral syphilis. For several weeks he had had a little dragging of his right leg. In 1898, while on a cruise in Cuban waters, he noticed that for periods of five minutes at a time he would lose his sight over one-half of his visual field; does not remember which half. He would be able to see only the half of objects, sign-boards, etc. These attacks of hemianopsia would clear up and recur many times in the twenty-four hours. They lasted for a month, and have never since returned. One evening, in October, 1899, while watching a game of billiards, he was seized with severe headache and went to bed. The next morning he had a severe attack in which he was cyanotic for hours. He was critically ill, the breathing light and quiet, and for some time it was not thought that he would recover. He remained unconscious for a week, his temperature being markedly subnormal. After consciousness returned he talked at random, and did not know where he was for a time. No paralysis followed. For some time before this attack he had had severe headaches at intervals. He gradually recovered, but during the convalescence he noticed that he had the most unquenchable thirst, which had persisted without interruption ever since, and for which he sought advice. Since the attack in October, 1899, his physical health had been excellent. He had had no headaches and was able to go hunting; but, as he expressed it, he "simply lived to drink." He said that he passed no moment without thinking about it. He literally drank quarts of cold liquids at a time. The urine had become markedly increased, and he passed from 9000 c.c. to 10,000 c.c. daily. No perspiration over body, but profuse sweating over forehead and face in hot weather. Next to his thirst the most distressing symptom at the time he came under observation was the existence of severe racking pains in the lumbar region, which were worse at night and interfered with his sleep. No treatment had been of any avail. He had taken potassium iodide up to 150 drops of the saturated solution in the day.

Physical Examination. Remarkably healthy looking man; good color and fine physique; weight 204 pounds. Arteries not sclerotic. Pulse slow, regular, and not increased in tension. Tongue red and clean. Pupils medium-sized, equal, react to light and accommodation; ocular movements perfect. Move-

ments of facial muscles normal; no trace of any residual paralysis. Hearing good. Taste and smell normal. No Romberg's symptom; stands well on either leg. Knee-jerks are slightly exaggerated. Tactile, thermic and painful sensations everywhere perfect. The examination of the thoracic and abdominal organs was negative. Ophthalmoscopic examination showed the disks to be clear. The margins were well defined. Arteries not sclerotic. No retinal changes.

Urine Examinations. While in the hospital the amount of urine daily ranged between 5970 c.c. and 6990 c.c. The urine was very pale; the specific gravity averaged 1003; there was no albumin, sugar or diazo. For a period of five days the nitrogen, urea, chlorides and phosphoric acid were estimated. All were within the normal limits. During this period the daily excretion of urine exceeded the intake of fluids by from 370 c.c. to 1100 c.c.

Treatment. The patient was put on antisyphilitic treatment, but during his short stay in the hospital there was no special improvement in the nervous or urinary symptoms.

In the following case no definite history of a primary luetic infection was obtained, but from his sexual history and the early improvement of the cerebral manifestations after the commencement of potassium iodid there seemed no doubt as to the existence of cerebral lues. Nonne records an almost identical case in which his diagnosis was "meningitidis luetica gummosa basalis; encephalomalachia aretriosklerotica (hemiparesis sinistra, hemiparalysis dextra, hemianopsia duplex, polydipsia):"

CASE III. (*Gen. Hosp.*, No. 33393). *Diabetes insipidus probably due to cerebral syphilis; initial symptoms were left-sided headache and pains in the legs; polydipsia preceded polyuria; marked excess of urine over fluids; decided psychical disturbances; severe vertigo and transitory attacks of left-sided hemiparesis, and later a definite right-sided hemiplegia; late history of hemianopsia attacks; improvement in general condition under potassium iodid; exaggerated knee-jerks; history of transitory attacks of hemianopsia.*

W. A., male, white, single, aged thirty-two years, stenographer, was admitted to the Johns Hopkins Hospital, under Dr. Osler, for the first time on January 6, 1901, complaining of headache, thirst, passing of large quantities of urine, and pains in the feet, left hip-joint and body.

The family history was unimportant. The only previous illness he had ever had was an attack of typhoid lasting thirteen weeks at the age of nineteen. He denied having had gonorrhea or syphilis, although he admitted excessive sexual indulgence of a promiscuous nature. He was a heavy drinker and for several years averaged a quart of whiskey daily.

His present illness began during the summer of 1898 with severe constant

headache over the left side of the head. This was soon followed by severe pains in the knees and legs. About two months after the onset of the headache his thirst became intense, and soon he noticed that he was voiding abnormally large quantities of urine. His appetite was usually rather poor. There was complete loss of sexual power and desire. He steadily lost weight and strength before admission. His mental condition seemed to have changed. In taking the history he would break out into violent tirades against his previous physicians and employers. He declared on several occasions that he had two heads, and was very boastful about the amount of work he was capable of performing.

Physical Examination. The important features of the physical examination were as follows: The patient was sparely nourished, weighing 140¼ pounds. There was no asymmetry of the skull or face. Complained of soreness on the left side of the head on percussion and on pulling the hair lightly. Percussion note on the left side of the cranium seemed a little higher pitched over the frontal and parietal regions. Left pupil was slightly smaller than the right; both reacted to light and accommodation. No strabismus or hemianopsia. There was no difference in the grip of the two hands or in the strength of the two arms. The flexor muscles of the left thigh were a trifle weaker than those of the right. Otherwise the muscular power of the lower extremities was equal. Romberg's symptom was present in a moderate grade. The triceps and radial reflexes were normal. Both patellar reflexes were distinctly exaggerated. The epigastric reflex was diminished, plantar increased and cremasterics normal. The lungs and heart were normal and abdominal examination was negative. There was no visible evidence of a scar on the genitalia. Dr. Randolph found that there was slight hyperemia of the left papilla and the disk outlines were rather vague. Right fundus was normal.

Urine Examination. The quantity of urine on his admission ranged between 5300 c.c. and 12,620 c.c.; the specific gravity between 1001 and 1004. It was persistently negative for albumin, sugar and casts.

A striking feature in the case was the almost constant and marked excess of fluids ingested over the urine output, this excess ranging from 400 to 6350 c.c. daily.

Treatment. The patient on admission was started immediately on potassium iodid in 15-grain doses three times a day, to be increased 5 grains every other day. This drug was given owing to the strong conviction that the cerebral manifestations were syphilitic in origin. There was immediate improvement in the headache and mental manifestations. The mental symptoms disappeared in two weeks, and when the patient left the hospital, on February 6, 1901, the headaches had entirely disappeared and he had gained 18¾ pounds in weight. Valerianate of zinc and ergotin were tried, with the object of reducing the flow of urine. Both seemed to reduce the urine somewhat, the latter to the greater extent. On potassium iodid alone the average daily output of urine for nine days was 10,100 c.c.; on potassium iodid together with 15 grains of valerianate

of zinc three times daily the average output for nine days was 9900 c.c.; on potassium iodid and 2 grains of ergotin three times daily the average output daily for the same period was 8100 c.c.

Second Admission. The patient was readmitted on June 17, 1901. On two or three occasions he had complained of numbness and heaviness in the left arm and leg. On the morning of admission, while coming down stairs, he suddenly experienced a sensation of heaviness in the left leg and arm. Both extremities felt as though they were asleep. He was forced to sit down on the steps. For two minutes he was unable to move either arm or leg. Five minutes later the strength had returned, and he felt perfectly well again. When he reached the hospital there was no evidence of muscular weakness and there was nothing on examination not previously noted. He had been taking 90 grains of potassium iodid three times daily. The urine had materially reduced. He remained in the hospital only five days, the daily quantity of urine ranging from 4960 to 6220 c.c.

Third Admission. The patient was admitted a third time on December 1, 1901. He had felt so much stronger that on November 21 he had taken up active stenographic work again. On November 28 he found on attempting to get out of bed at 10 A. M. that he had practically no use of his right leg. Later in the day he lost the power of his right arm, and articulation became difficult. When he entered the hospital four days later there was still almost entire loss of power on the right side, including the lower facial muscles on the same side. Articulation was still indistinct. The eye-grounds were normal. The amount of urine on this admission ranged between 5700 c.c. and 9180 c.c. daily. There had been considerable return of muscular power when the patient left the hospital on December 21.

Since that date the patient has frequently been seen. When he reported in March, 1902, he gave a history of hemianopsia attacks. He stated that at times in going along the streets he would be able to see only the half of objects, such as signs, etc. The last time he was seen was about five months ago. He was able to get about with a cane without much difficulty, but he still dragged his right foot considerably. His general health was excellent and his weight had increased to over 170 pounds. The thirst and polyuria were less intense, but still persisted.

The cerebral features in Case IV., with their rapid disappearance on the administration of potassium iodid, together with the early relief of the marked polyuria and polydipsia by the use of the same drug, seem to leave no doubt as to the diagnosis. It was, in fact, the only case in which the potassium iodide had any marked effect in reducing the polyuria. An interesting feature in the case was that, notwithstanding the reduction of the urine

from 16,000 c.c. to between 2000 c.c. and 3000 c.c., the specific gravity remained extremely low, being always below 1005.

CASE IV. *Diabetes insipidus, probably of syphilitic origin; passage of two renal calculi two years before onset; symptoms of polyuria preceded by headache for three or four months. Disease supposed to have followed an attack of influenza; marked loss of weight and extreme asthenia. Distinct vertigo and ataxia; double abductor paralysis of the vocal cords. Paralysis of the right palatal muscles; early diminution of thirst and urine under potassium iodid, and later an extraordinary gain in weight and strength under the same treatment.*

E. F. B., white, male, aged thirty-six years, single, mechanical engineer, consulted me on July 14, 1900, complaining of general weakness and loss of voice.

The family history was unimportant. Patient had pneumonia at nineteen. Eight years ago he complained of "rheumatic" pains in hips and shoulders. Right-sided colic two years ago, when he passed two calculi the size of buckwheat grains. Smoked to excess, but drank in moderation. Gonorrhea at twenty-two, but denied syphilitic infection. For two or three years the patient had been engaged in Northern Michigan as a mining engineer.

The present illness began in the fall of 1899 with severe headaches. In January, 1900, he had what was believed to be an attack of influenza accompanied by considerable fever. About this time he began to pass enormous quantities of urine and suffered from a perfectly insatiable thirst. Dr. Charles Drummond, of Painesdale, Houghton County, Michigan, wrote me that repeated examinations of the urine showed it to be very pale, with a specific gravity of from 1003 to 1005. It never contained sugar nor albumin. The patient measured his urine shortly after the onset of the polyuria and found that the quantity was four gallons, or 16,000 c.c. for the twenty-four hours. He lost 30 pounds in two weeks at the onset. His appetite was poor from the beginning. Dr. Drummond put the patient on potassium iodid and ext. cinchona comp., which apparently had a marked beneficial effect, for by May 1, 1900, the thirst and polyuria had almost entirely disappeared, and at the time he came under observation he did not have to void at all during the night. Since the "influenza" attack he had remained very weak. He had no cough, but was very dyspneic. Seven weeks ago his voice began to grow husky, and the hoarseness has persisted. In drinking there was a tendency for the fluid to return through the nostrils. For two weeks he had suffered from severe nausea and vomiting. Vomits just after rising in the morning. Headaches still appear at times. Had not taken potassium iodid for several weeks.

Physical Examination. When the patient first came under observation on July 14, 1900, the following were the most striking features: The patient was moderately emaciated; weight 130 pounds. Voice husky. Dyspneic on the slightest exertion. Right palatal muscles and pillars of the fauces are paralyzed.

Dr. Warfield reported a bilateral abductor paralysis of both vocal cords. Pupils equal and react sluggishly to light and actively to accommodation. Movements of eyeballs good. No hemianopsia. Dr. Mills found the eye-grounds to be normal but reported some existing astigmatism. Romberg's symptom fairly well marked, the body swaying toward the left. Knee-jerks markedly exaggerated. Scar on the right side of neck resulting from a suppurating gland which was opened three years ago. The examination of the thoracic and abdominal viscera was negative. There was no evidence of a scar on the genitalia. Some fluid mucoid sputum was obtained and was negative for tubercle bacilli.

Urine Examinations. A fresh specimen of urine voided at the first visit was of a very pale color; neutral; specific gravity 1002; negative for albumin, sugar and casts. The urine for July 24th and 25th measured only "five pints and one gill," or approximately 2600 c.c. It was pale; acid; 1005; no albumin, sugar or casts. On August 12 to 13 it measured 2000 c.c., the specific gravity being 1004. During the same day he drank 3000 c.c. of fluids.

Treatment. The patient was first placed on a liberal nutritious diet and $\frac{1}{40}$ grain doses of strychnin three times daily. When seen on August 15th there had been no material improvement in his general condition, and owing to the suspicious character of the cerebral manifestations I decided to start him on potassium iodid again, beginning with 15 grains three times daily and gradually increasing until he reached 30 grains to the dose. His general health began to immediately improve. The nervous features gradually cleared up with the exception of the laryngeal symptoms. His appetite and strength rapidly improved, and when he was seen October 8, six weeks later, his weight had increased from 131½ to 157 pounds, a gain of 25½ pounds. The patient then left the city, with instructions to take 30 grains of potassium iodid three times daily.

Shortly afterward he was sent to London, England, by a Philadelphia electric firm to look after their interests there. While on a visit to the United States in April, 1903, he called to see me. His general health was excellent. He then weighed 167 pounds. He thought he still drank more fluids and voided more urine than he should, but did not consider that either was much increased. His voice was a little husky. There was no ataxia and the knee-jerks were normal. A fresh specimen of urine showed the same features as previously. The specific gravity was 1004. It was not possible to ascertain the twenty-four hour amount.

The therapeutic test in this case suggested very strongly that the cerebral manifestations were probably syphilitic in origin. The improvement in the nervous features began promptly on the administration of potassium iodid. The case is of further interest in that the polyuria and polydipsia were markedly relieved by the giving of the drug in the early stages by Dr. Drummond. Not-

withstanding the striking diminution in the polyuria and the reduction of the output to between 2000 c.c. and 3000 c.c., the specific gravity remained low, ranging between 1002 and 1005.

The syphilitic lesion may be a gumma, involving some portion of the base of the brain, particularly the floor of the fourth ventricle. Occasionally a basilar meningitis and a gumma may be associated, as in one of Nonne's cases. In Case V. the polyuria was undoubtedly due to lues. Of the existence of a gumma there can be no doubt. The response to antisyphilitic treatment was magical. The nervous features practically entirely cleared up with the exception of the optic atrophy, and there was an appreciable reduction in the polyuria and thirst.

CASE V. (*Gen. Hosp., No.* 42792). *Diabetes insipidus of syphilitic origin; definite evidences of cerebral gumma; intense right-sided headaches; ptosis of right eye; complete right-sided blindness; complete paralysis of all the branches of the right third nerve; prompt relief of cerebral symptoms on administration of potassium iodid; complete disappearance of ptosis and third nerve paralysis; moderate diminution of thirst and polyuria.*

M. C. S., white, female, widow, aged fifty-seven years, was admitted to the private ward of the Johns Hopkins Hospital under Dr. Osler's care on May 17, 1903, complaining of severe neuralgia in the right side of the head.

The family history was unimportant. Of the diseases of childhood she remembers only having had scarlet fever. At that time the left ear was in some way affected and she has had partial deafness in it ever since. She had typhoid fever at fifteen. As a young girl she had severe attacks of headaches and biliousness associated with constipation. Otherwise she had never had any serious illnesses previous to the onset of her present symptoms. There was nothing abnormal in her menstrual history. She was married at twenty years and had borne four children, all of whom are living and well, their ages ranging between twenty-seven and thirty-seven. She had had two miscarriages, one twenty years ago and the other between the birth of her third and fourth children. Her husband died one year ago. The cause of death could not be definitely ascertained. His general health had been, so far as known, good. He drank heavily and was only occasionally at home. The patient had never suffered from bone or joint pains, skin eruptions, falling out of the hair, or sore throat. After one of her miscarriages she was ill in bed for two weeks. There was no definite history of a luetic infection obtainable. She had always been constipated. For eight or ten years the patient had voided rather frequently, and she thought that the amount of urine was increased in amount. There had been no increased thirst, however.

Her present trouble began in November, 1901, nineteen months before admission, with sudden onset of pain in the right side of the head, especially just behind the right ear. There was also some pain in the right cheek and temple and to a lesser extent in the right side of the neck. The pain was of a throbbing character, and was paroxysmal in its occurrence, although it never left her entirely at this time. In August, 1902, while at Atlantic City she was free from the pain for three weeks. In November, 1902, the pain in the head became much more severe, and the patient also began having disturbances in taste and smell. Food tasted and had the odor of putrefying meat. This sometimes produced nausea. About this date she first noticed dimness of vision of the right eye, and within one month complete blindness developed in this eye. She never had much pain in the eyeball itself, the pain being more deeply seated in the head. In March, 1903, she noticed that her right upper eyelid began to droop, and within a short time complete ptosis developed. Paralysis of no other facial muscles was noticed. There had been a progressive loss in weight and strength. During the present illness there had been a gradual increase in her thirst and in the amount of urine voided. She does not know which developed first. She has to void four or five times during the night at the present time. Her skin had felt harsh, but there had been no itching. There have been no sensory symptoms whatever. Four weeks before admission an attempt was made to drain the frontal sinus through the nose with a view of relieving the pain, but without any material subsequent improvement.

On May 19th Dr. McCrae made the following note: The patient has a rather anxious expression. There is no great emaciation. The gums and mucous membranes are rather pale. There is complete ptosis of the right eye, none of the left. The pupils are unequal, the right being larger than the left, and does not respond to light. The left pupil does not react to light. There is slight movement outward and downward of the right eyeball. The tongue is protruded in the median line. The grasp of both hands is weak, but there is no definite paralysis on either side. The pulse is of good volume, regular, 72 to the minute. The vessel wall is slightly sclerosed.

The thorax is somewhat rounded. The percussion note is rather hyperresonant throughout. The respiratory sounds are everywhere feeble, but seem clear. The heart sounds are clear throughout and of normal relative intensity.

The abdomen is rather full; nowhere tender. Over the trunk there are numerous somewhat raised areas, some of which are pigmented and resemble senile warts. Others resemble fibromata, and still others xanthomata. The liver dulness seems about normal; the edge of the liver is not felt. The spleen is not palpable. The right kidney is readily felt, but apparently is not enlarged; left not felt.

There is no edema of the ankles. The knee-jerks are present but seem diminished.

On May 19th Dr. Mills made an ophthalmoscopic examination and reported as follows: There is atrophy of the right optic nerve. The left disk is rather pale. All branches of the third nerve on the right side are paralyzed. The sixth nerve is unaffected.

Dr. Thomas made the following neurologic note on May 20th: The patient's sense of smell is fairly good; she recognizes the odor of milk and of asafetida. Vision: right eye, *nil;* left eye, is able to read large letters at the top of the *New York Herald,* but not smaller print. Fields of vision roughly tested—some restriction of the temporal field. The right eye is completely closed, and she is unable to open the eye in the least. The left eye is steady and the eyeball is freely movable in all directions. In looking upward there is an associated movement of the occipitofrontalis on the left and also on the right side, the latter occurring first. The left pupil in a moderately bright room is about 3.5 mm. in diameter and reacts directly to light and accommodation. It does not react consensually to light. The right eye is held toward the outer canthus and cannot be moved toward the middle line. In looking up there is no movement; in looking down there is slight rotation with the upper axis rotated in. The right pupil is about 6 mm. in diameter. It does not react to light, consensually or directly, nor during accommodation with the left eye. There is no contraction during forcible closure of the eye. Pinching of the skin on the right side of the neck does not cause any change in the size of the pupil.

The muscles of mastication seem to act equally on both sides. The facial muscles act equally well on the two sides. The sensation to touch, pain, heat and cold seems equal on both sides and about normal in acuteness. She does not hear a loud ticking watch in direct contact with the right ear but hears it a foot away on the left side. The muscles of the palate act well and equally. Pharyngeal reflex is equal on the two sides. The tongue is protruded in the median line. There is no apparent weakness on either side of the body. The sensation in the hands and arms and the stereognostic sense seem good. The muscular strength of the legs tested in bed seems normal.

The deep reflexes are present and are normal. Plantar irritation causes flexor response. Cutaneous sensation is apparently normal.

Urine Examination. The urine for the twenty-four hours from May 18th to 19th measured 6700 c.c. It was extremely pale, very turbid, without any precipitate, faintly acid, specific gravity 1002; no albumin; no sugar. On microscopic examination there were no casts, but a few squamous epithelial cells and numerous bacteria.

The daily quantity of urine during her three weeks' stay in the hospital ranged between 3990 c.c. the lowest, and 6720 c.c. the highest amount. The quantity more frequently approached the latter than the former. For one week the intake of fluids was compared with the output of urine, and the two were found to approximately balance. There was an excess of 790 c.c. of fluids over urine during this period, however.

Our suspicions were so strong that the cerebral symptoms were due to a syphilitic gumma that the patient was immediately placed on daily mercurial inunctions and potassium iodid. She was started on 40 grains of the latter three times daily, and the dose was steadily increased until on June 8th, the day of discharge, she was getting 165 grains daily. The antisyphilitic treatment produced almost immediate relief to the cerebral symptoms. The intense headache in the right side of the head rapidly disappeared, and she had been entirely free from it for ten days previous to her discharge from the hospital. On leaving the hospital on May 17, 1903, she could raise her right upper eyelid so that the palpebral orifice measured about 1 cm. Her general health had also materially improved. Up to the time that the patient left the hospital there had been no material diminution in the polydipsia or polyuria. The amount of urine voided for the last twenty-four hours was 4660 c.c.

On May 5, 1904, Dr. Claytor, of Washington, under whose care the patient now is, kindly furnished me the following information regarding her: She continued the use of the potassium iodid until four months ago, or for six months after leaving the hospital. The headaches have never returned, and she feels perfectly well so far as her general health is concerned. Her present weight is 160 pounds, being a gain of 39 pounds since she left the hospital. The ptosis of the right eye has entirely disappeared. There is slight external strabismus of the right eye, but the movements of the eyeball are perfect, the axis of the right following that of the left in all directions. The sight of the right eye is entirely lost; there is not even light perception. For a week or two one of her feet has been swollen; the condition appeared to be rheumatic. Her thirst was diminished, but she still drank one quart of water at night and voided approximately four liters of urine in the twenty-four hours. She was of the opinion that she voided on an average less urine than a year ago.

Heijden reported a case of diabetes insipidus in a patient with chronic hydrocephalus. Cases have followed otitis media, probably from meningeal involvement. The disease has been observed in *general paresis*, imbecility and chronic mania.

Diseases of the spinal cord have in rare instances been regarded as the cause of the polyuria. Schlesinger met with it in a patient with *tabes dorsalis*. Westphal observed it in *spastic spinal paralysis*. In this instance sugar was present in the urine at first, but afterward disappeared. Instances of persistent polyuria have been observed by Kraus in syringomyelia and by Friedrich in hereditary ataxia.

As instances in which the diabetes insipidus has been attributed to reflex action from stimulation of certain nerves may be men-

tioned the cases of Hadra and Ralfe, in which the disease was associated with *aneurysms of the carotid and abdominal aorta*, respectively. Here, probably, the reflex action was through the vagus.

Diabetes insipidus has not infrequently been associated with diseases of the abdominal viscera. As early as 1794 Frank observed a fatal case in a patient with chronic disease of the intestine. Schapiro has reported five similar cases. Dickinson recorded a case in a patient with *carcinoma of the liver with involvement of the solar plexus.* At the autopsy it was found that there were carcinomatous metastases in the retroperitoneal lymph glands, which involved branches of the solar plexus. There was also a marked hyperemia of the kidneys.

Polyuria is not an uncommon symptom in *hysteria, epilepsy, tetanus* and *chorea*, and it reaches such a grade, and has been so persistent in some of the cases, that many observers have been inclined to consider them cases of diabetes insipidus. Such instances have been observed by Oppolzer, Kien, Buttersack, Külz and others.

The following case was evidently due to some brain lesion of obscure nature. It may possibly have been luetic, but the history was not sufficiently definite to warrant its being placed with the luetic group:

CASE VI. (*Gen. Hosp., No.* 35321). *Diabetes insipidus of doubtful origin; typhoid fever eight months before onset; unconsciousness and left-sided convulsive movements of the arm and leg preceded the thirst and polyuria; amount of fluids exceeded that of urine; night urine greater than that during the day; knee-jerks diminished.*

J. W., male, white, single, aged twenty-five years; German, laborer in a copper foundry, was admitted to the Johns Hopkins Hospital, under Dr. Osler, on June 28, 1901, complaining of intense thirst and the passing of enormous quantities of urine.

Family history unimportant. The patient was a laborer in a copper foundry, where the air was foul and dusty. In August, 1899, he was treated for double tertian malaria in the Johns Hopkins Hospital. On September 24, 1900, he was again admitted, suffering from a mild attack of typhoid fever. He was discharged just a month later. There was no polyuria at that time. In April, 1901, he was suddenly seized with unconsciousness, and said that during the unconscious spell he was told that he had convulsive movements in the left

arm and leg. The left eye was in some way affected and he had ringing in the left ear. He had suffered from severe headaches previous to the unconscious attack. Heavy drinker, taking from fifteen to twenty glasses of beer daily. Tobacco in moderation. Denied both gonorrhea and syphilis.

The present illness began four weeks before admission. He first noticed intense thirst, followed shortly afterward by the voiding of large quantities of pale urine. The urine for one twenty-four hours measured 3¾ gallons (15,000 c.c.). There had been no headaches nor vertigo since the onset of the diabetic symptoms. His eyesight in the left eye was slightly defective, and he complained occasionally of seeing double at night.

Physical Examination. The patient was fairly healthy looking and weighed 140½ pounds. There was no facial asymmetry; movements of facial muscles good. Skull seemed normal. Pupils normal in size and equal; reacted to light and accommodation. No strabismus or hemianopsia. Dr. Reik reported that there were curious changes about the bloodvessels of the fundus oculi that were unexplainable. There were some minute deposits about the retina and choroid suggestive of what one sees in diabetes mellitus. The examination of the thoracic and abdominal viscera revealed nothing abnormal. The inguinal and epitrochlear glands were slightly enlarged. No evidence of a scar on the genitals. Knee-jerks diminished, just obtainable on reinforcement. Distinct Romberg's symptom. Marked ataxia in walking, following a line with difficulty. Slight inco-ordination of the movements of both upper extremities. Blood count: red cells, 4,312,000; leukocytes, 11,300; hemoglobin, 65 per cent.

Urine Examination. The urine during the patient's stay in the hospital was enormously increased, the amounts ranging from 7330 c.c. to 13,330 c.c. for the twenty-four hours. The daily average was 10,002 c.c. It was extremely pale, faintly acid in reaction, the specific gravity ranging between 1000 and 1003, the former specific gravity being observed on several occasions. Albumin, sugar and casts were constantly absent.

The daily averages of the fluids ingested and of the urine voided for the twenty-four hours were 10,543 c.c. and 10,002 c.c., respectively, for twenty days, showing that the daily average of fluids ingested exceeded that of the urine voided by 541 c.c.

Owing to the strong suspicion that the cerebral symptoms were probably of luetic origin the patient was placed on increasing doses of potassium iodid, so that when he left the hospital on July 19 he was receiving 30 grains three times daily. When he was discharged there was no material improvement in his condition, the amount of urine for the last twenty-four hours being 11,520 c.c.

Cases VII., VIII. and IX. which follow, together with Case I., comprise the four cases in which no definite etiologic factor could be ascertained, and which I have classified as idiopathic cases. Case VII. presented a feature of interest in the fact that

he had bilateral xanthoma palpebrarum on the upper lids. A careful study of his metabolism was made and the results have been reported elsewhere.* The point of interest brought out was that during eighteen days he took on 49.77 grams of nitrogen, and yet weighed 200 grams less at the end than at the beginning of the period.

CASE VII. (*Gen. Hosp., No.* 21086). *Diabetes insipidus of doubtful etiology; probably belongs to the idiopathic group; disease of ten years' standing; polydipsia the initial symptom; bilateral xanthoma palpebrarum; double suppurative otitis media; history of edema of the feet; study of metabolism showing marked excess of nitrogen intake over output, with a slight loss of weight.*

A. S., white, male, aged forty-four years; married, barkeeper, was admitted to the Johns Hopkins Hospital, under Dr. Osler, on November 1, 1897, complaining of dyspnea, weakness, intense thirst, and the passage of large quantities of urine.

The family history was unimportant. The patient had always been a healthy man previous to the onset of the symptoms of diabetes insipidus. Three years ago he was operated on for fistula-in-ano and for three years he had had a double suppurative otitis media. For many years he had been a barkeeper and had taken on an average from ten to twelve glasses of beer daily. He denied ever having contracted syphilis or gonorrhea.

The present trouble began with insatiable thirst ten years ago. He would drink four or five gallons of fluid daily and often as much as a quart at a draught. The polydipsia was immediately followed by polyuria. Seven years ago he began to notice swelling of the feet. This had not been present for the last three years. He had had cough and dyspnea for three years. The patient had never had any cerebral manifestations. He complained occasionally of his arms and legs "going to sleep." At the onset his weight was 230 pounds. He has since lost 60 pounds.

Physical Examination. The patient was a stout man, weighing 177 pounds on admission. He was healthy looking. On each upper eyelid there was a large, flat xanthoma measuring 1.75 x 0.75 cm. The lungs were emphysematous, and his heart was dilated and showed distinct evidences of myocarditis, the two conditions accounting for his cough and dyspnea. The abdominal examination revealed normal conditions. The triceps, radial and patellar reflexes were moderately exaggerated. The cutaneous reflexes were normal. The fundi were negative, but there was a double suppurative otitis media. The blood count showed a slight polycythemia. The red cells were 5,960,000; leukocytes, 9000; hemoglobin, 96 per cent.

* For fuller reports of Cases II., III., IV., VI. and VIII. see Johns Hopkins Hospital Reports, vol. x. p. 198.

Urine Examination. During a stay of about ten weeks in the hospital the urine ranged between 3790 c.c. and 6740 c.c. The specific gravity was never extremely low, the ranges being 1005 to 1009. The urine was always pale, and was persistently free from albumin, sugar and casts.

A series of metabolism experiments were carried out on this patient, and the results have been elsewhere reported. The most striking feature brought out was that the patient took on 49.77 grams of nitrogen during a period of eighteen days and yet weighed 200 grams less at the end than at the beginning of the experiment.

Zinc valerianate was tried as a therapeutic remedy in this case, but without beneficial results. The patient was discharged practically unimproved, so far as his diabetic symptoms were concerned, on February 3, 1898.

Case VIII. possibly had some cerebral disease, but the symptoms were not at all definite. He had a pigmentary choroiditis, and ophthalmoscopic examination showed incipient optic nerve atrophy. The patient is likely to come under observation again, and it will be interesting to note whether the cerebral symptoms progress or not. The existence of subcutaneous fibroid nodules is worthy of note in this case.

Case VIII. (*Gen. Hosp., No.* 45118). *Idiopathic diabetes insipidus; duration, three years; history of defective vision since childhood; pigmentary choroiditis on ophthalmoscopic examination; very marked general contraction of the field of vision; incipient optic nerve atrophy; subcutaneous fibroid nodules of the fibro-lipomatous type.*

B. R., male, white, single, aged thirty years; iron-worker, was admitted to the Johns Hopkins Hospital December 28, 1903, complaining of headache, pains in the muscles and bones, and frequent micturition.

His father died of heart disease at forty-eight; mother of tuberculosis at thirty-four. Her maternal grandmother and a maternal aunt both died of tuberculosis. One sister died at thirty-four of heart disease following rheumatism. A paternal aunt had carcinoma of the breast.

The patient had measles, scarlet fever, mumps, smallpox and whooping-cough when a child. In 1899 he had typhoid. Four years ago he noticed nodules develop beneath the skin of both forearms; they have persisted up to the present. He had dysentery in Cramp's shipyard, in Philadelphia, in 1901. In July, 1903, he had an attack of malaria. During this same month he had a sunstroke, and he has suffered a good deal from headaches since. The patient was treated in the Johns Hopkins Hospital (Gen. Hosp., No. 35293) in June, 1901, for a bronchitis which he had suffered from ever since he had an attack of influenza, about Christmas, 1900. Since he had his attack of smallpox at

four years of age he has at intervals had a discharge from his left ear. His vision as long as he can remember has been defective and the field limited. The ocular symptoms seemed worse since the sunstroke attack. For three years he has been troubled a good deal with bronchitis. He drinks whiskey and beer moderately. He chews and smokes tobacco. He had an attack of gonorrhea in 1894, but denied ever having had syphilis, and no definite history of the disease could be obtained.

The patient's present illness began between two and three years ago. He first noticed frequency of micturition. He had complained of this symptom in June, 1901, when he was previously in the medical wards for bronchitis, but the largest amount of urine for the twenty-four hours at that time was only 620 c.c. and the lowest specific gravity 1014. The polyuria apparently came on after this date. It was soon followed by increased thirst. Both these symptoms have gradually become worse up to the present time. His appetite became ravenous. He would stop eating, not because his hunger was satisfied, but because he "felt he could not hold any more." Recently he has felt less energetic, and little matters worry him more than formerly. He has suffered a good deal from headache, backache and pains in the bones and joints. His right leg has felt numb and cold. In walking he would often go about on the tips of his toes, not feeling capable at times of putting the heel to the ground. Occasionally he has a tendency to trip up, and says that his gait is unsteady. He has not lost weight, but on the contrary has apparently gained. On his first admission he weighed 146, and he now weighs 176 pounds.

Physical Examination. (Dr. Campbell Howard.) The patient is a large-framed, healthy-looking man. Face is considerably scarred from smallpox pits. Pupils are equal and react to light and accommodation. No tophi in the ears. The mucous membranes are of good color; tongue clear; teeth good. Over the flexor surfaces of both forearms there are several, subcutaneous, firm, inelastic, painless tumors varying in size from a nickel to a fifty-cent piece. There is also one at the bend of the left elbow. The skin over the largest is a little reddened, owing to slight dilatation of the capillaries.

The thorax is very large and deep anteroposteriorly. Expansion is good and equal on both sides. Percussion and auscultation are clear throughout both lungs.

The point of maximum cardiac impulse is difficult to locate on inspection and palpation. The sounds are best heard in the fourth interspace well inside the left mammillary line. The relative cardiac dulness is normal in extent. The heart sounds are distant and feeble, but clear at the apex and base.

The abdomen is very prominent but symmetrical. Some fulness in either flank. There are a few scattered capillary angiomata. Superficial veins not dilated. In the lower part of the left iliac region there is an early fibroid nodule. No abdominal tenderness; walls everywhere elastic; no muscle rigidity. The percussion note is dull in both flanks, but does not change with posture. The

liver dulness is normal in extent; border of liver is not felt. Spleen not palpable.

The knee-jerks are diminished, but are obtained on reinforcement.

On the day of admission Dr. Mills made an ophthalmoscopic examination, and reported as follows: Both eyes show disseminated choroiditis. There is incipient optic nerve atrophy. Floating opacities throughout vitreous humor of both eyes. In the left eye there is a retinal hemorrhage on the outer side of the disk. Right eye, V=18/40; left eye, V=18/30 with an effort.

On December 30 the field of vision for white was tested, and it was found to show very marked general contraction in both eyes, the left being more affected than the right. There was no permanent or temporary hemianopsia made out at any time during the patient's stay in the hospital.

The blood count on January 2, 1904, was as follows: Red blood corpuscles, 6,400,000; leukocytes, 7600; hemoglobin, 88 per cent.

On January 13 a careful sensory examination was made for pain, touch and heat and cold and no disturbances found.

The blood pressure was estimated twice during the patient's stay in the hospital. The systolic pressure on both occasions was 130 mm. Hg and the diastolic 100 and 80 mm. Hg with Dr. Erlanger's blood-pressure apparatus.

Urine Examinations. The urine was measured daily throughout his stay in the hospital, and the daily intake of fluids also. The average amount of urine for seventeen days was 5420 c.c., the lowest daily excretion being 3340 c.c. and the highest 8020 c.c. The average intake of fluids was 6300 c.c., being 880 c.c. more than the average excretion of urine; the lowest intake was 5250 c.c. and the highest 7800 c.c. The urine was always of a very pale straw color; the specific gravity was never extremely low, the lowest being 1005 and ranging between this and 1010, on one occasion the average being 1007. The reaction was always faintly acid. At no time were albumin, sugar or casts found. The centrifugalized sediment showed a few pus cells.

During his stay in the hospital the patient had an acute pharyngitis and tonsillitis. The output of urine was smaller during this time than at any other period during his stay in the hospital.

For the last few days that the patient was in the hospital he was placed on tincture ergot, gtt. x, three times a day. It, however, had not had any effect in diminishing the amount of urine. He was discharged at his own request on January 15, 1904, in practically the same condition as on admission.

Owing to the impossibility of determining at all definitely the etiology in this case, it was deemed best to place the case in the idiopathic group. The existence of incipient optic nerve atrophy suggested, however, possible cerebral disease.

No definite etiologic factor could be ascertained in Case IX. The luetic infection with secondary symptoms ten years ago leads

to the suspicion that lues may have been the cause. The evidence was too indefinite, however, to place the case anywhere but in the idiopathic group.

CASE IX. (*General Dispensary, No.* 320534). *Diabetes insipidus of doubtful origin and consequently placed in the idiopathic group; possibly due to syphilis, however.*

W. H. C., male, white, aged thirty-four years; married, granite cutter, was admitted for treatment in the Johns Hopkins Dispensary on April 21, 1902, complaining of excessive thirst and the passage of large quantities of urine.

The family history was unimportant, and none of the other members were similarly affected.

The patient did not remember having had any of the usual diseases of childhood. He had inflammatory rheumatism ten years ago. Seven years ago he had gonorrhea and three years before this he had a "chancre." He had sores in his mouth some time after the appearance of the initial lesion. He was under treatment for syphilis for two and a half years. Up to one year ago he took about three alcoholic drinks daily, but since the onset of his present illness he has not taken any alcohol. He smokes and chews moderately.

His present illness began in February, 1901, fourteen months ago. He noticed first that he had to get up frequently at night to urinate and passed large quantities of colorless urine. His thirst increased rapidly and was intense. He says that since the onset he passes between three and four gallons daily, and would fill a slop-jar during the night. From the beginning he has suffered from intense lumbar pains. He occasionally has neuralgic pains about the right eye, and at times some headache. He sleeps badly. At intervals he is subject to nausea, and occasionally he vomits. These symptoms are apt to occur in the early morning. Previous to the present illness he perspired freely on active exertion, but now the only place where he perspires is about the forehead. His appetite has remained unchanged. Bowels are regular. He has gained in weight.

Physical Examination. The patient is of medium height, rather stout and weighs 170 pounds. General appearance good. Lips and mucous membranes of good color. Tongue clean. The pupils are equal and react to light and accommodation. There is no hemianopsia on rough examination. No Romberg's symptom. There is no general glandular enlargement. Slight pulsation of the vessels of the neck.

The thorax is well formed and symmetric. Expansion good and equal. The lungs are clear throughout on percussion and auscultation. The point of maximum cardiac impulse is neither visible nor palpable. The sounds are feeble and best heard in the fifth interspace in normal position; they are clear at the apex and base.

The abdomen looks natural. Panniculus abundant. The liver, spleen and kidneys are not palpable.

The examination of the genitalia reveals a distinct scar about one centimeter in diameter just behind the corona of the glans penis on the left side.

The knee-jerks are slightly exaggerated.

Urine Examination. The urine on the day on which he came under observation was perfectly colorless. The reaction was faintly acid and specific gravity just 1000. There was no albumin, sugar or casts. The patient made several visits to the dispensary until August 27, 1902. During this time he measured his urine carefully on several occasions, the amounts being 12,500, 16,500, 12,500, 10,000, 11,500 and 13,000 c.c. Specimens always showed the specific gravity to be between 1000 and 1002 and to be free from albumin and casts.

While he was under treatment in the dispensary he was given potassium iodide and mercury without any change in the amount of the urine, but an improvement in his general health. He gained fifteen pounds during the five months he was under observation. In August, 1902, he left the city, and has not been seen since.

From the foregoing it will be seen that apparently a large number of etiologic factors enter into the causation of diabetes insipidus. Our experience, in finding four out of nine cases in this series to be due to syphilis, may have been unusual, but it has convinced us that syphilis is a more frequent cause than is generally believed by the profession. Whether the case belongs to the idiopathic or the symptomatic group it matters not. The determining factor is a disturbance of a secretory function of the kidneys. Gerhardt[15] says that in idiopathic diabetes insipidus "the disease is due to a disturbance of the secretory function of the kidneys and not to an increase in the thirst or to blood changes." He draws an analogy between the polyuria in this disease and the hypersecretion of the gastric juice in functional disturbance of the stomach. Osler says that "it results from a vasomotor disturbance of the renal vessels, due either to local irritation, as in the case of an abdominal tumor, to cerebral disturbance in cases of brain lesion, or to functional irritation of the center in the medulla, giving rise to continuous renal congestion."

SYMPTOMATOLOGY. 1. *Polyuria.* The most characteristic and constant symptom of the disease is the increase in the amount of urine eliminated. Trousseau had a patient, aged twenty-four years, who voided 43 liters in a day. In a few instances the

weight of the urine voided daily practically equalled the weight of the patient. Van der Heijden reports an instance of a girl, aged six years and weighing nineteen and one-half pounds, who passed daily from fourteen and one-half to nineteen and one-half pounds of urine, and Vierordt cites an instance of a child weighing 13.2 kilograms voiding 12.3 kilograms of urine daily. The largest quantity of urine passed by any of the cases in this series was 16.5 liters. The amount passed at an individual voiding may be enormous. Thus one of our patients passed 1700 c.c. at one voiding. The urine is always extremely pale, often as colorless as water, of fairly acid reaction, and of a low specific gravity, the latter usually ranging between 1060 and 1005. It is to be remembered, however, that when the urea elimination is high the specific gravity of the urine may remain practically normal. Thus Laparguois observed a case in which 6 liters of urine were passed daily, with a specific gravity of 1017. The urine rarely contains albumin. Occasionally a trace may be present at intervals. Sugar and casts are absent. There has been a good deal of work done to determine whether the patient with diabetes insipidus eliminates the fluid taken more quickly than the healthy individual; in other words, whether a condition of "tachyuria" or "bradyuria" exists. The opinions of those who have investigated the subject vary. Falck, Neuschler, and A. Pribram believe that bradyuria occurs, and F. Kraus holds the opposite view. E. Pribram has endeavored to settle this disputed point, and he is led to conclude that bradyuria exists. The majority of those who have investigated this matter, then, are of the opinion that after a large draught of fluid the increase in the flow of urine takes place more quickly, and the elimination is more rapid in the healthy individual than in the person suffering from diabetes insipidus.

In most cases the amount of urine voided is less than the amount of fluids ingested. In certain instances it appears that the urine may be in excess of the fluids ingested, even when the fluid in the solid food is taken into consideration. It is thought that individuals may absorb moisture from the air. Dickinson found that one patient between the acts of micturition (no food or

drink being taken in the interval) gained, respectively, fifteen and one-half ounces in three hours, and nineteen and three-quarter ounces in five hours. As a rule, more urine is voided during the night than during the day.

The following statements may be made regarding the constituents of the urine:

(*a*) The *urea* is usually excreted in normal amount. It may be increased to 70 or 80 grams daily. These are the so-called azoturia cases. Where the nitrogen is increased in diabetes insipidus cases it is practically always due to the increased ingestion of proteids rather than to increased tissue destruction.

(*b*) The *sodium chlorid* is usually normal, but occasionally it is markedly increased.

(*c*) The *phosphoric acid* elimination varies, but is usually within normal limits.

(*d*) *Albumin* is almost universally absent. It may occur occasionally in a case, just as it is believed to do at times in apparently healthy individuals.

(*e*) *Sugar* is absent. A number of cases have occurred where a diabetes insipidus has passed over into a diabetes mellitus, and *vice versa*.

(*f*) *Inosite* has occasionally been found in the urine. It has no practical importance in the disease. Its occurrence is believed to be due to the washing out of the inosite from the muscular tissues by the enormous amounts of fluid taken. It has been found in the urine of healthy individuals after they have taken large amounts of water to drink.

2. *Thirst* is practically constant. It is the symptom which usually attracts the patient's attention first. The question whether in diabetes insipidus the polyuria or polydipsia is primary has been a much disputed one. The majority of observers, including the most recent, incline to the view that polydipsia is primary. Nothnagel's case[16] is usually cited as a typical instance of a primary polydipsia. A man was kicked in the abdomen and fell against a stick of wood, striking his head in the region of the right ear. He was not rendered unconscious, but was dizzy. Half an hour after the blow the patient developed intense thirst and drank 3

liters of water, and it was not until about three hours later that the first urine was voided. The thirst is sometimes perfectly insatiable, and, as one of the present series expressed it, he "simply lived to drink." When the patients have been cut off from water they have frequently drunk their own urine. The amount of fluids taken may reach the enormous total of 50 liters daily, as in Trousseau's case. Buttersack gives the following conditions as indicating a primary polydipsia in any particular case: 1. There is normal sweat secretion. 2. The urine is less than the amount of fluids. 3. The polyuria ceases on cutting off the fluids drunk. 4. The urine elimination and the amount of liquids taken run parallel.

3. *Absence of sweating* is the customary rule. The insensible perspiration is also diminished. This has been found by Strauss, Flatten and Strubell. The formula for determining the insensible perspiration during a given period is as follows: Weight at the beginning + intake — weight at the end + output = insensible perspiration. It has been found to be about half that in a normal individual.

4. The *appetite* is usually poor. Nausea and vomiting are not infrequent. Occasionally the appetite is enormous, as in Trousseau's case, where a patient with diabetes insipidus frequented a restaurant where the bread was not charged for, and was paid by the restaurant keeper to stay away, owing to the enormous quantity of bread that he ate.

5. *Constipation* is the rule. This is due to the absorption of fluids from the intestinal tract.

6. *Ocular changes* occur. Cataract has been noted. Case VII. had double xanthoma palpebrarum. Case VIII. had a pigmentary choroiditis. Cases III. and VIII. had incipient optic atrophy, and Case V. advanced optic atrophy of the right eye, with total blindness on that side.

7. *Headache* is often a very distressing symptom. It is most marked in the cases with cerebral disease, but occurs even in those without. It was a striking symptom in 6 of our 9 cases.

8. *Lumbar pains* of a very intense character are often present.

9. *Impotence* very frequently occurs, but occasionally returns in the luetic cases in which improvement in the nervous features occurs.

10. *The blood* shows but little change. Strauss and Stoermer found the specific gravity increased. The blood count varies but little from the normal. There was slight polycythemia in one of our cases, the red cells being 6,400,000 per c.mm.

11. *Loss in weight* occurs frequently at the onset. It is most rapid and marked in the secondary or symptomatic cases. Often there is no loss of weight for years in the idiopathic cases.

12. *Edema of the feet* is a rare symptom, but has been described. It usually occurs in the late stages of the disease in the asthenic, emaciated cases. There was a history of it in 2 of our cases.

13. Unlike diabetes mellitus, the *knee-jerks* are often exaggerated. In the present series they are exaggerated in 5, normal in 1, diminished in 2, and not noted in 1.

14. *Metabolism* does not seem to be much disturbed, notwithstanding the excessive flushing of the tissues with fluids. Most of the features in connection with the metabolism have been referred to under Division 1. In 1 of our cases (No. VII.*) I made a study of the metabolism during a period of eighteen days. The nitrogen balance-table showed that the patient added 49 grams of nitrogen to his body during this period, and yet weighed 200 grams less at the end than at the beginning of the period.

PROGNOSIS. The course of the disease is largely dependent upon whether the case belongs to the idiopathic or the secondary group. In the idiopathic form the general health is rarely impaired to any great extent. The patients lose weight for a few weeks after the onset, but later they retain their weight, and many of them look comparatively healthy and robust. This form has been known to last for fifty years. If the diabetes be due to some organic disease of the brain or of the abdominal viscera, the patients are liable to lose weight rapidly, and the general health quickly becomes impaired. Death is much more likely to take place at an early date in these cases than in the idiopathic ones.

* For a full report of the studies of metabolism in this case, see the Johns Hopkins Hospital Reports, vol. x. p. 218.

The duration of life is largely dependent upon whether certain vital structures are involved or not.

DIAGNOSIS. Chronic interstitial nephritis with abundant pale urine of a low specific gravity may very closely simulate diabetes insipidus. Careful and repeated examinations of the urine, with the finding of traces of albumin and a few hyaline and granular casts, should readily differentiate the former. The absence of sugar and the low specific gravity exclude diabetes mellitus. The question as to whether the disease should be differentiated from the hysteric polyurias seems to be a debatable one. In many of the monographs on diabetes insipidus the polyuria of hysteria is included as one of the clinical forms. Usually it is placed in the symptomatic group. Personally I am opposed to this conception. In these cases the disease the patient is suffering from is hysteria, of which the polyuria is a symptom. As a general rule, the hysteric polyuria is transitory, and there are usually nervous and psychical phenomena present which render the cause of the polyuria clear. It must be admitted, however, that it is difficult to draw a hard-and-fast line between the two affections. Some writers have attempted to classify those cases in which thirst is the first symptom as a separate and independent disease, applying the name "primary polydipsia" to these cases. The advisability of recognizing these cases as constituting an independent disease seems doubtful, for, as we have seen, it appears probable that the polydipsia antedates the polyuria in most cases of diabetes insipidus.

TREATMENT. The treatment is most unsatisfactory. It is useless to restrict the amount of fluids, as it only distresses the patient and causes no permanency in the diminution of the polyuria. The great number of drugs that are recommended in this disease is ample evidence of the general inefficiency of the therapeutic remedies used. Preparations of opium have been used with some benefit. The relief is probably due to the lessening of the sense of thirst. The commonest sedative in use is valerian. Either the powdered root, given at first in 5-grain doses three times daily, and increased until the patient takes as high as 2 drachms daily, or the valerianate of zinc in 15-grain doses increased

to 30 grains three times a day, may be administered. Ergot, in various preparations, has in some cases given fair results. The bromides, salicylates, and antipyrin have been tried, but the results on the whole have been unsatisfactory. Galvanization of the spine has been advocated. W. F. Clark used adrenal extract with benefit. In one of our series it was given, but failed to produce beneficial effects.

In cases suspected of being due to syphilitic disease of the brain potassium iodid or mercury, or both together, should be given a good trial. All four of our syphilitic cases showed marked improvement in the cerebral manifestations and in the general health, with striking gains in weight. In only one case was there any marked diminution in the polyuria; in another the diminution was slight. I know of no instance in which the polyuria has entirely disappeared under potassium iodid. The good effects of the drug are manifested in the relief of the nervous features and in the improvement in the general health. The polyuria may be lessened, but too much must not be expected from the drug in this direction.

SUMMARY. Experiments on dogs and rabbits have taught us that a simple polyuria is produced most frequently by lesions of the brain in the following situations: (*a*) By injury of a point in the floor of the fourth ventricle a little anterior to Claude Bernard's glycosuric center. (*b*) By injuries to various portions of the middle lobe of the cerebellum. (*c*) By lesions of the corpus trapezoides of the pons and the lateral part of the exposed portion of the medulla oblongata. In rabbits a permanent polyuria follows lesions in these situations, as demonstrated by Kahler. These areas of the rabbit's brain correspond in the human brain with the portions of the pons where the sixth and seventh cranial nerves make their exit at the base.

Clinically we recognize two groups of cases of diabetes insipidus: (*a*) The idiopathic or essential cases—those without evident cause. (*b*) The secondary or symptomatic cases—those referable to some organic lesion or due to some recognizable cause. There are certain border-line cases in which it is difficult to say to which group they belong.

Tumors of the medulla and floor of the fourth ventricle, cerebral traumatism, including cerebral hemorrhage and basilar meningitis are the commonest organic lesions causing the disease. Whereas our experience in this series may have been unusual, it would strongly indicate that cerebral syphilis is a cause in a much larger percentage of cases than is generally supposed. The syphilitic lesion may be a gumma, but it is probably often a basilar syphilitic meningitis. A recurring or fugitive bitemporal hemianopsia in a case of diabetes insipidus is strong evidence in favor of the disease being due to syphilis and of the lesion being a basilar syphilitic meningitis. When one reflects how easy it is to produce polyuria experimentally by various injuries at the base of the brain, it is not difficult to understand why a basilar meningitis of syphilitic origin may also produce a polyuria in man.

In fifteen years there were 7 cases of diabetes insipidus admitted to the Johns Hopkins Hospital and Dispensary out of a total of 403,535 patients admitted to all departments of the institution, or 0.001 per cent. of the total. Of 17,042 cases admitted to the medical wards under Dr. Osler there were 6 cases, or 0.03 per cent.

Of the 9 cases here reported 4 belonged to the idiopathic group and 5 to the secondary or symptomatic group. All of the latter showed very striking cerebral manifestations, and 4 of them were undoubtedly syphilitic in origin.

Thirst appears to be the first symptom complained of in the majority of cases, and the balance of opinion favors the view that polydipsia precedes the polyuria in most of the cases. The knee-jerks are usually exaggerated, contrary to the usual findings in diabetes mellitus. In our 9 cases they were exaggerated in 5, diminished in 2, normal in 1, and not noted in 1. All the cases with exaggerated knee-jerks had cerebral manifestations. As yet no striking and constant metabolic disturbances have been found.

We are still very much in the dark as to the true nature of the disease. It seems to be caused by " a vasomotor disturbance of the renal vessels, due either to local irritation, as in the case of abdominal tumor, to cerebral disturbances in cases of brain lesion, or to functional irritation of the center in the medulla, giving rise to a continuous renal congestion " (Osler).

There is no constant anatomical finding at autopsy characteristic of the disease. The most frequent changes are enlargement of the kidneys, congestion of the vessels and dilatation of the tubules. In the secondary or symptomatic cases the organic lesions causing the disease are variable.

The prognosis is good in the so-called idiopathic cases, the disease not tending to shorten life. It is graver in the symptomatic cases, emaciation and general weakness often developing rapidly. Death may occur early in the latter group.

The treatment in the majority of cases is very unsatisfactory. Opium, ergot, and valerian may effect an improvement, but the benefit is usually temporary. The cases which appear to do best are those of luetic origin. Antisyphilitic treatment usually promptly relieves the cerebral manifestations and improves the general health and nutrition (Cases III., IV., and V.). Although potassium iodide may cause a decided diminution in the polyuria and polydipsia (Cases IV. and V.), it is seldom that these symptoms are completely relieved. Too much must not be expected from the use of antiluetic remedies from this standpoint, however. We are more likely to help the polyuria and thirst in the cases due to lues than to any other cause. The most striking effects, however, are manifested in the improvement in the cerebral manifestations and in the gain in weight after the patients have been placed on the antisyphilitic treatment.

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DISCUSSION.

DR. BAUMGARTEN: I am interested in the question whether Dr. Futcher's observations tend to explain in any way the connection between diabetes insipidus and saccharin diabetes. I observed a case fifteen or twenty years ago in a young man without any previous history of disease, without any hereditary predisposition, who developed a polyuria of high degree, with a urine of very low specific gravity, constantly free from sugar, which lasted for six months. He was a muscular man, doing a great deal of hard work. His condition became so serious that he was compelled to give up his work. After a period of several months of relief he came to me with a recurrence of the polyuria, and this time the urine contained abundant sugar. Periods of copious excretion of sugar recurred again and again during the six years that I watched him. It was a clear case of saccharin diabetes, and yet it had begun with an immense polyuria without the slightest trace of sugar. There was never in his history any suspicion or evidence of syphilis, nor in the history of his parents. I have heard that he died of tuberculosis of the lungs.

DR. THOMSON: A case was admitted some years ago to my wards that was of interest to me on account of the excessive polyuria. I had all the liquid and food he swallowed during the day weighed in order to determine whether he was passing more water from the bladder than he was taking into the system, and for two or three weeks he seemed to get rid of more water than he was taking in by the mouth. The man died suddenly and we found him the subject of a miliary tuberculosis, but it is curious that he did not have any symptom of cerebral trouble.

In another case, that of a physician, where I was particular to inquire as to the history of syphilis, he denied positively that he had ever been in the way of contracting syphilis. The only feature in his case was the hereditary one.

DR. TYSON: In an experience extending over many years I have been consulted several times in private practice, perhaps six or seven, by cases of diabetes insipidus, and one of the interesting features was that they were so frequently relieved by potassium iodid. It was quite usual to see the polyuria diminish under this treatment, though not always cured. The most interesting of these cases I have still under observation. The patient consulted me as a boy of twelve years; he is now twenty-two years of age, and during the time of his illness he passed enormous quantities of water daily. I am afraid to say how much. He seems to have been completely cured. His father was a dissipated man, and may have had syphilis, and the son some degree of specific meningitis which caused the symptoms. At least this is the only way of accounting for the good influence of the potassium iodid.

DR. DOCK: I wish to speak of the prognostic differences of these cases. Generally it is very cheering to begin the treatment of the cases with a history of syphilis, because they usually do well. I have a case under observation, however, that illustrates how hopeless some of them are when the polyuria is associated with more advanced lesions. A man aged forty years had the common history of venereal sores not recognized as syphilitic and never treated constitutionally. Three years ago he had a hemiplegia, quickly recovering, followed shortly by partial blindness, and then by polyuria. When I first saw him he was passing eight liters of urine a day. On account of the marked optic atrophy, as shown by the ophthalmoscope, I had little hope of doing much for him. Large doses of potassium iodid and inunctions of mercury had absolutely no effect upon the urine, though the blindness seems less marked than before treatment was begun, six weeks ago.

DR. JACOBI: The frequency of that symptom is, I believe, much greater than the hospital records would justify, for the reason that diabetes insipidus is frequent in childhood. Twenty-five per cent. of all the cases, perhaps more, occur under ten years. I have seen quite a number of cases that, without any other cause, followed chorea minor and hysteria, also some following whooping-cough; in these cases it was attributed to cerebral hemorrhage. I have seen a certain number of boys from seven to eight to thirteen years of age with the history of a fall upon the occiput; also a few cases connected with and very probably depending upon tumors; one after sunstroke. The cases among infants and children are numerous. They are not admitted to general hospitals, and that is why it appears to be much less frequent than it really is. In protracted eneursis of children diabetes insipidus should be suspected.

In all the cases where I had any particular reason to attribute the symptom to anything but lack of proper circulation I have given atropin with good results, combined or not with ergot. In others strychnin was successful; opium rarely.

DR. FUTCHER: I did not wish to give the impression that the vast majority of cases of diabetes insipidus are due to lues, but merely that there are a greater number of cases due to that disease than has been generally supposed. There are many other causes for diabetes insipidus, and I would like to speak of one cause that has a bearing upon the cases reported by Dr. Fussell this morning of polyuria following typhoid fever. We had a case that had been treated for typhoid, and some three months later came back with polyuria and marked symptoms of diabetes insipidus. Whether there was any connection with the typhoid I do not know but there have been a good many cases of diabetes insipidus associated with diseases of the small intestines.

THE CLINICAL FEATURES OF CEREBROSPINAL MENINGITIS, OR CEREBROSPINAL FEVER OF THE EPIDEMIC TYPE.

By HENRY KOPLIK, M.D.,
OF NEW YORK CITY.

During the past few years additional interest has been given to the study of cerebrospinal meningitis of the epidemic form, due mainly to the investigations, on this side of the Atlantic, of Councilman and his pupils, Osler and others. A severe epidemic of this disease in Boston (somewhat over a hundred cases) has given Councilman an opportunity to study thoroughly the disease from an epidemiologic as well as from a pathologic standpoint. Osler has been able to study a number of cases occurring in an outbreak in Baltimore.

During the past five years there have been yearly outbreaks of this disease in New York, culminating in an extensive epidemic in the spring of this year. I have thus been able to study quite a number, some 37 cases, of the disease at the bedside, and to analyze carefully its clinical features. In this study I have utilized 77 cases of meningitis occurring in my service in the Mount Sinai Hospital, New York. These 77 cases were divided into the following groups: 37 cases of cerebrospinal meningitis of the epidemic type, 21 of which were substantiated by culture and cover-glass spread to be due to the meningococcus intracellularis. Of the remaining cases of the epidemic form, some were not substantiated by lumbar puncture, being clinically self-evident; others were so-called dry taps; 35 cases were of the tuberculous form of meningitis, as substantiated absolutely either by postmortem or guinea-pig experiment, or by discovery of tubercle bacilli in the puncture fluids. One case was a so-called staphylococcus meningitis; 1 case, primary pneumococcus meningitis; 1 case streptococcus meningitis. In 2 cases, so-called pseudoinfluenza bacilli were found.

In the above statistics I have not utilized 15 cases of cerebrospinal meningitis which belong to the epidemic of the present year. Of these 15 cases, 5 died; of the remaining 10, 5 are still in my ward, 1 being comatose. Some of these cases were so classic and self-evident, or the symptoms improved so steadily, that they were not subjected to lumbar puncture. The ultimate fate of the cases remaining cannot be stated as yet.

AGE. The ages of the patients affected with epidemic cerebrospinal meningitis confirm the assertion that this affection is a disease of young people, 60 per cent. of the cases being under two years of age; the youngest was four months old; 77 per cent. of the cases were under four years of age, the oldest child being fourteen years. The average age was two years. In tuberculous meningitis, however, the average age was somewhat higher, only 41 per cent. of the cases being under four years of age, the average age being four years and four months.

CLASSIFICATION. In looking over the literature on the subject of meningitis, the most lucid classification is given by Osler. He divides the classification into primary and secondary forms, which will be accepted by all. The primary forms include cerebrospinal fever, both of the sporadic and the epidemic types, and as a separate disease the pneumococcus meningitis. In the secondary forms he includes the tuberculous, the pneumococcus meningitis, the latter being secondary to pneumonia, endocarditic disease, or injury of the cranial bones. Third, there are the pyogenic forms, due to staphylococci, the streptococci, or secondary either to disease of the cranium or to local affections. Fourth, are met the forms secondary to typhoid fever, influenza, diphtheria, gonorrhea, anthrax actinomycosis. Fifth, Osler would include in a separate rubric the so-called serous-meningitis, which, I may say, is to-day being recognized as a secondary form of the disease, due possibly to infection by streptococci or pyogenic organisms. This classification, it will be seen, recognizes both the sporadic and the epidemic forms of cerebrospinal fever as being the same disease and due to the same essential cause.

My own cases are of the primary form of cerebrospinal fever of the epidemic type, including at least one form which may occur sporadically, the so-called posterior basic meningitis of Still.

BACTERIOLOGY. The bacteriologic features of my cases were worked out in the laboratory of the Mount Sinai Hospital, under

the supervision of the pathologic staff. Referring to a report of this work by E. Libman, published in the *Mount Sinai Hospital Reports* of this year, it will be seen that all the cases were examined culturally. Reliance was not placed on cover-glass stain alone. All the cultures corresponded to those described by Weichselbaum. None of them, however, showed gram positive diplococci. There was a variation in the growth on media not containing serum; but when this growth was obtained on such media it was never profuse.

The conclusion is that there is one type of the diplococcus meningitis in the New York cases of cerebrospinal meningitis. This type corresponds to that found by Councilman and Wright in Boston, Osler and Hirsch in Baltimore and Herrick and others in Chicago. Both the nasal discharges and the conjunctival secretions were studied, and in one of my cases the presence of the meningococcus was proven to be present culturally in the conjunctival inflammatory discharge. In this case there was a distinct history of conjunctivitis preceding the attack of meningitis, and the diplococcus was also established in the cerebrospinal fluid. We have never proven the presence of the meningococcus in the secretions and discharges of the nose. We have found, however, the micrococcus catarrhalis, an organism which closely resembles the meningococcus, the cultural characteristics of which we will not enter into, but refer the reader to the extensive investigations of this organism by Dr. Celler, my former assistant, and published in the *Mount Sinai Hospital Reports* of this year.

Clinical Types. The clinical picture presented by children suffering with cerebrospinal meningitis of the epidemic type is quite characteristic, not only in its onset but in the general course of the disease. I have been able to differentiate certain distinct types in the cases occurring in my hospital service and consulting practice. Previous to the present epidemic in New York the malignant cases during the past four years have not been as common as they were during the present year. I have recently seen a number of cases presenting the malignant form in which children in previous good health are attacked with the disease and die within twenty-four or thirty-six hours.

The following case, one of the first of this year's epidemic, is quite a characteristic example of this type of the disease: An infant, twelve months old, nursed at the breast, perfectly formed,

a large, healthy, bright child, never previously affected by any illness, nursing and bowels normal. On the morning previous to the day on which I saw the case with the family physician the child appeared sleepy and stupid and refused the breast. It vomited, but was not feverish. That evening the physician was called in and found the infant quite drowsy and listless, with a temperature of 103°, pulse 110 and very weak. There was no peculiarity about the eyes, no stiffness of the muscles of the neck or body. At 3 and 5 A.M. on the following day the child awoke crying, and the mother discovered some red spots on the cheeks. The face was slightly swollen, the eyes staring and the child was apparently blind. By 8 A.M. the entire face, hands and body were covered with blotches which turned bluish; the tissues of the extremities seemed to be hard and swollen; the buttocks and body looked as if the child had been beaten, ecchymosis being quite extended over the body and extremities when I saw the child. At this time the temperature was 101° and the pulse very weak, scarcely to be felt at the wrist; the lips were blue; the reflexes abolished. When I saw the child a few hours later it had no rigidity of the muscles of the neck; there was no Kernig symptom; the pupils were uneven and did not react; there was a slight conjunctivitis; an examination of the lungs, abdomen and ears gave a negative result. The breathing was irregular and catchy, the pulse very rapid and scarcely to be felt at the wrist. The diagnosis of cerebrospinal meningitis was confirmed by a lumbar puncture made postmortem, a cloudy fluid, milky in color, being drawn off and the intracellular diplococcus of Weichselbaum being found in the fluid, both by stain and culture.

Since seeing this case I have seen at least 3 others, each presenting similar features. In two of these rapidly fatal malignant cases the hemorrhages thus mentioned were preceded by an erythematous rash.

Another type of cerebrospinal meningitis is more commonly met with in which a child in apparent health is suddenly taken with dizziness or vertigo, vomiting follows, accompanied by severe headache, and then the child passes through the different phases of the disease which are well known and described in books on the subject.

A more puzzling type of cerebrospinal meningitis in infants and young children is that in which a child in apparent health is suddenly found to have a temperature, is restless, refuses the breast,

vomits once or twice, and then for weeks will run an intermittent type of temperature as high as 104° or 105° F., falling to the normal or subnormal daily. In the intervals of freedom from temperature the children or infants will play, and then when the temperature rises they may complain of slight headache, become drowsy, irritable and refuse nourishment. In these cases the typical signs of meningitis are not always present. The delirium may not be constant, or may not extend over the twenty-four hours. The rigidity at the back of the neck may not be very marked, especially in young infants. In these cases, also, the children may not have a marked Kernig symptom, especially if below two years of age. The most characteristic feature about these cases, it seems, is the prolonged period of temperature of an intermittent type, closely resembling malaria. In fact, the attending physician in many of these cases has examined the blood for the malarial plasmodium or attention has been drawn by the intermittent type of the temperature to the ears in the hope that some focus of suppuration would be found. In other words, these infants and children may continue over a period of weeks with this peculiar temperature, and the onset of the disease has not been marked by convulsions or any of the classic symptoms of meningitis; and still a lumbar puncture in these cases will reveal the presence of the intracellular meningococcus in the fluid thus obtained.

In young infants the type of the disease most commonly met with is that in which the onset is sudden, marked with general convulsions, high fever, vomiting at the outset, the high fever of the intermittent or remittent type, continuing over weeks. After the fever has lasted for some days or weeks the mother will notice the rigidity of the head, the irritability of the child and the marked emaciation.

THE MODE OF ONSET. In all the cases that I have had an opportunity to study in hospital service in which the diagnosis was confirmed the main characteristic of the onset of the disease was that it was abrupt. Observation has shown that children in apparent health would suddenly be attacked by the symptoms just detailed. In only a small percentage of cases has there been a doubtful history of the sudden onset. In this respect the disease differs markedly from the meningitis of the tuberculous type, which is of slow onset, and in only a small percentage of cases is such a history doubtful.

NECK RIGIDITY. Great stress has been laid by some authors on the presence or absence of neck rigidity. As has been hinted, there are some cases in which rigidity is not present at all times, but if these cases are observed for any length of time our experience shows that slight or marked rigidity is present at one time or another in all cases of cerebrospinal meningitis. Opisthotonos is present in about 70 per cent. of the cases. In the posterior basic forms, of which we will speak later, the rigidity and episthotonos is so marked that the child will assume the position seen in tetanus, being perfectly rigid, curved backward, the forearms extended, the fingers clenched in the palms; these are cases which only form a small percentage of the total number seen in an epidemic, and they affect mostly younger infants and children. According to Osler, neck rigidity or opisthotonos was not present in the adult form of primary pneumococcus meningitis. Rigidity was present in my own case of primary pneumococcus meningitis, confirmed by autopsy. In our case not only was rigidity present, but also opisthotonos.

REFLEXES. In a majority of cases of epidemic cerebrospinal meningitis the skin and tendon reflexes were present in the early stages of the disease, but were apt to disappear in the rapidly fatal cases or in moribund cases.

THE BABINSKI REFLEX. Babinski, a French neurologist, described the extension of the great toe on irritation of the plantar surface of the foot as a characteristic sign of disease of the pyramidal tracts or the lateral columns of the cord, and we have studied this sign in the forms of meningitis coming under our notice. We have found that in meningitis of the epidemic cerebrospinal type it was present in 4 of the 25 cases studied. This is in marked contrast to what is found in tuberculous meningitis, in which this reflex was absent in only 6 cases of the 26 in which it was sought. In other words, it was present in 77 per cent. of the cases of the tuberculous form of meningitis, and I regard the presence of this reflex as a valuable addition to the clinical picture of tuberculous meningitis as distinguished from cerebrospinal meningitis of the epidemic type. I can only explain its constancy in tuberculous meningitis by the fact that in these cases there is possibly an invasion, either directly or indirectly, of the pyramidal tracts of the lateral columns of the cord by the disease. The sign is of very little value, however, in children and infants below two years of age, for it may at times

be seen in perfectly normal infants or in those suffering from various affections. This seems also to be the conclusion reached by Morse, of Boston, who contends that the Babinski sign is quite inconstant in its manifestations in infants and children below two years of age.

THE KERNIG SYMPTOM. Much has been written about this very interesting symptom, the contraction of the flexor muscles of the lower extremities, as seen in cases of meningitis. I have found that the Kernig symptom is of very little utility in infants and children below two years of age. Of course, in infants, especially under one year, there is a normal tendency toward myotonia. Even superficial observation will show that normal infants are apt to lie with their lower extremities flexed, assuming very much the position of the fetus in utero. In children below two years of age suffering from meningitis the irritability is so great that it is impossible to come to any conclusion as to the presence or absence of the Kernig symptom. In all the cases of cerebrospinal meningitis of the epidemic type above two years of age, therefore, the Kernig symptom was present. In cases of tuberculous meningitis, its presence was not so constant, being absent in 8 cases of 26 in which it was sought. I do not lay too great stress upon the presence of the Kernig as a pathognomonic sign of meningitis. It may be present in cases of which we are accustomed to say that there are cerebral symptoms without meningitis, as in typhoid fever or pneumonia.

HYPERESTHESIA AND MENTAL IRRITABILITY. In the majority of cases of epidemic cerebrospinal meningitis, after the usual symptoms have set in and the disease is well inaugurated, the children, and even infants, are irritable, refuse to be comforted, start at the least sound in the room, lie mostly on the side, the arms and lower extremities flexed, the body taking the crouching position. Any attempt to disturb the patients is met with resistance. In the present epidemic, although many cases have been exceedingly mild, hyperesthesia of the surface, and irritability of the mind were very marked in all cases. In past epidemics of 21 cases hyperesthesia of the surface was quite marked in fully 62 per cent. of the cases.

In marked contrast to the above is the absence in the tuberculous form of the disease of any reaction or hyperesthesia of the surface. The child lies in a stuporous condition, does not notice its surroundings; whereas in the epidemic cerebrospinal menin-

gitis, when not comatose, the children are alive to their surroundings, or are irritated by some things passing on around them. In the tuberculous forms of meningitis, hyperesthesia was present in only 3 of 34 cases. In other words: it was absent in 90 per cent. of the cases.

THE MACEWEN SIGN. MacEwen has pointed out that in children in various forms of meningitis we obtain on percussion a hollow note over the anterior horn of the ventricle. If the head is so held that the anterior frontal or parietal bone may be percussed over the situation of the anterior horn of the ventricle, this note will be produced. That is, if the patient sits upright and the head is inclined to one side, percussion of the inferior frontal or parietal bone will give a tympanitic note.

I have found that in 17 cases of tuberculous meningitis in which this note was sought, that it was present in 11, and it has seemed to me to be exceedingly valuable in making up the clinical picture of the tuberculous forms of meningitis. MacEwen thinks that the note is caused by the presence of fluid, so-called hydrocephalus, in the ventricle. In meningitis of the epidemic cerebrospinal type, however, this note is not obtained in the majority of cases. In 13 studied with this object in view it was present in only 2, showing the difference in this respect between the two forms of meningitis. In other words, if MacEwen is correct, there is very little distention of the ventricle with fluid in the first stages of the disease. In the chronic cases with increase of fluid in the ventricles, however, and these are the cases in which the note was obtained—I have found quite a marked MacEwen present.

FACIAL PARESES. As is well known, facial paresis is quite a constant feature of the tuberculous forms of meningitis, and in 35 absolutely substantiated cases of tuberculous meningitis it was found in 19 early in the disease, and it appeared toward the close in most of the cases. In epidemic cerebrospinal meningitis, however, facial paralysis occurs only in the severest types of the disease where the intracranial pressure to one side or the other, especially at the base, is quite great, and in 21 cases in which it was looked for, facial paralysis, marked or slight, was present in only 3 cases.

TEMPERATURE. One of the prevailing types of fever in children in the cases we have observed was that of the intermittent type, in which the temperature would be quite high at some time of the day,

and normal or subnormal at another. The range of temperature would sometimes be very marked, four, five, six or eight degrees. In one case which I have under observation of the basic form of Still, the temperature reached fully 106° to 106.5, falling to the normal or subnormal at some time during the day. The fever curve in this disease cannot be said to be characteristic, and at times will exhibit the widest irregularities.

THE SKIN. In most of my cases I have not been able to find the prevalence of the rashes described by most authors. This is due, possibly, to the fact that in the epidemics I have observed skin rashes and eruptions were not common. On the other hand, herpes, referring especially to herpes of the lip, is also not very common, and was present in only 2 of 20 cases. In the adult, however, Osler has found petechial erythematous rash, or herpes, in 13 of his 21 cases. In the epidemic of this spring I have observed a number of cases in which a roseola closely resembling that seen in typhoid fever was present. Lately a number of cases with a profuse petechial rash have been observed by me at the outset of the disease.

EYES. Contrary to what is the generally accepted opinion, we have found that expert examination of the fundus revealed no changes in the optic papilla in the majority of our cases of cerebrospinal meningitis, although in some there was dilatation of the veins or congestion without neuritis. In only one case was there descending neuritis. In a group of 26 cases of meningitis of the tuberculous variety examined by our expert, Dr. Gruening, some change was found in fully 77 per cent. of the cases. This change consisted either of an optic neuritis or papillitis, or the presence of tubercles in the choroid. In this group of 20 substantiated cases of tuberculous meningitis, 7 showed tubercles in the choroid. It would seem, therefore, that the condition of the fundus, aside from the positive discovery of choroid tubercle, gave us important presumptive evidence of the nature of the meningitis.

THE BLOOD. Every case of meningitis coming under our observation, including those of the cerebrospinal epidemic type, has been examined with reference to the leukocytosis present. The leukocyte count in all of our cases was made at intervals of three days in the course of the disease. In all of the cases of epidemic cerebrospinal meningitis there was leukocytosis to some extent. The leukocytosis was of the polynuclear type, the leukocytes

ranging from 20,000 to 55,000, exceeding 25,000 to the cubic millimeter in fully 55 per cent. of the cases. The lowest leukocyte count in any case was 11,100 to 12,000 to the cubic millimeter.

This corresponds very closely to what was found by Osler to be true of the adult cases. In the tuberculous forms of meningitis in infants and children we have not always found a so-called leukopenia. On the contrary, in fully 40 per cent. of the cases there was a leukocyte count of 20,000 to 25,000 to the cubic millimeter and under 20,000 in 60 per cent. of the cases. In no case, however, did the leukocyte count exceed 24,000, except in one case of tuberculous meningitis, in which we obtained a leukocyte count of 32,000. This leukocyte count which has just been mentioned (with the exception of the one last referred to) having been made in 26 substantiated cases of the disease, would seem to be an important feature, if we compare it to what is true of the adult. In Osler's cases of tuberculous meningitis leukocytosis was absent in only 3 cases; his highest count (24,333) corresponds so closely to what we have found true of our own cases in infants and children that we are apt to be led to the conclusion that a higher leukocyte count in tuberculous meningitis is exceptional, and, if higher, would speak more for a meningitis other than tuberculous in any given case.

I have studied the leukocyte counts in both the cured and fatal cases with a view of determining whether any conclusion as to prognosis could be drawn from the results of a leukocyte count. In six cases which recovered we had the following results:

CASE I. Six years of age. Observed from the fourth to the eighteenth day of the disease. Leukocytes, 16,800 to 24,000. Puncture fluid clear.

CASE II. Twenty months of age. Observed from the fifth to the fortieth day. Leukocytes, 15,000 to 45,000; the latter toward the twenty-first day of the disease. Puncture fluid clear.

CASE III. Four and one-half years of age. Observed from the fifteenth to the eighty-fifth day of the disease. Leukocytes, 15,000 at the outset, 34,000 at the midperiod, 21,000 in the convalescence. Puncture fluid turbid.

CASE IV. Five months of age. Leukocytes, 20,000 to 22,000. Puncture fluid clear.

CASE V. One year of age. Observed from the fifth to the fiftieth day. The leukocytes, 14,000 to 28,000, the latter in the midperiod of the disease; 15,000 toward convalescence. Puncture fluid clear.

CASE VI. Two years of age. Admitted on the fourth day of the disease with a leukocyte count of 40,000. Puncture fluid clear.

Taking a like number of fatal cases, we had the following counts:

CASE I. Four months of age. Observed from the twelfth to thirty-seventh day of disease. Leukocyte count from 17,600 to 23,200, the low count at the close of the disease. Puncture fluid thick and turbid.

CASE II. Four months of age. Observed from the twelfth to the twenty-ninth day of the disease. Leukocyte count from 32,600 to 34,000. Puncture fluid cloudy.

CASE III. Six years of age. Observed from the fifth to the fourteenth day of the disease. Leukocyte count, early, of 30,000. Puncture fluid purulent.

CASE IV. Three years of age. Observed from the ninth to the eighteenth day, with a leukocyte count ranging from 34,000 to 55,000 Puncture fluid cloudy.

CASE V. Ten months old. Observed over six weeks. Leukocyte count from 10,600 to 26,000; the latter toward the close. Puncture fluid turbid.

CASE VI. Aged six months. Observed from the twelfth to the forty-seventh day of the disease. Leukocytes, 28,600 to 17,600 early in the disease, and 9800 to 18,200 later on; the lower count at the close of the disease.

It may be stated that in the so-called basic cases in infants and young children, the leukocyte count early in the disease may range from 32,000 to 34,000, but toward the close, when the temperature rarely rises above the normal, the leukocyte count may fall as low as 9800 to 10,600. In this respect the leukocyte count resembles what is found in cases of tuberculous meningitis, and these cases, on account of this, have been mistaken by some for tuberculous meningitis. The leukocyte count in the fatal cases in which the fluid obtained by lumbar puncture is quite turbid, with a sediment resembling pus, is apt to be high, mounting to 35,000 to 55,000.

On the other hand, fatal cases, with a thick turbid fluid on puncture, may give a count not exceeding 23,200.

Cases which have recovered showed a leukocyte count of 14,000 to 28,000. During the course of the disease the leukocytes may have mounted as high as 45,000, as in one case on the twenty-first day of the disease.

It cannot therefore be said that a prognosis as to the recovery or fatal issue can be made from the leukocyte count alone, without taking into account the duration of the disease and the characters of the lesion as revealed by clinical methods of precision.

CHARACTERISTICS OF THE CEREBROSPINAL FLUID OBTAINED BY LUMBAR PUNCTURE. So much has been said of the physical characteristics of the fluid obtained by lumbar puncture in cases of meningitis, either of the epidemic cerebrospinal, the tuberculous, or the suppurative forms, that the writer scarcely deems it proper to repeat what has been said upon this subject. The cytology of the fluids obtained by lumbar puncture in cases of cerebrospinal meningitis is of particular interest as regards the possibility of making a diagnosis from the elements found in the fluid alone, apart from the bacteriology. Of 13 cases studied with reference to the cytology, 9 showed a preponderance of polynuclear leukocytes and 4 showed mononuclear cells as prevailing elements. It would seem, therefore, that in the majority of cases of cerebrospinal meningitis of the epidemic type the lumbar fluid presented a polynuclear leukocytic picture. In 15 cases of tuberculous meningitis studied with a view to noting the character of the cell elements, 14 showed a prevalence of the mononuclear cells, and one case an equal number of mononuclear and polynuclear cells. In the above studies all the fluids were subjected to careful centrifuge.

It would seem, therefore, that in tuberculous meningitis there is a prevalence of mononuclear cells, and that this is so constant that it would seem to us to be characteristic, and verifies what is known from publications on this subject. It will be seen, however, that there are cases of cerebrospinal meningitis of the epidemic type, three of which we have noted, in which there is a cytologic picture closely resembling that seen in tuberculous cases. In chronic cases, instead of a predominance of polynuclear cells in the sediment of the fluid obtained by lumbar puncture, the mononuclear picture is apt to present itself, closely resembling what is seen in the tuberculous cases. This is especially true of

the chronic cases of cerebrospinal meningitis of the basic type described by Still. Bendix explains this variation from what might be called the normal picture in cerebrospinal meningitis by the fact, proven by Ribbert, that in chronic inflammations lymphocytes abound in the transudates; whereas, in acute inflammations, leukocytes abound.

It seems to us that the physical characteristics of the fluid obtained by lumbar puncture aid us but little in coming to a conclusion as to the form of meningitis present. In cerebrospinal meningitis of the epidemic type we have obtained fluid which has been quite clear, with scarcely any sediment, cloudy varying to the purulent fluid; whereas in the tuberculous forms of meningitis the fluid was clear in 72 per cent. of our cases, but was quite cloudy in others, and more or less cloudy in the remaining number of cases. In all the epidemic cerebrospinal cases which we consider as substantiated either by the clinical picture or the results of lumbar puncture, the diplococcus meningitis was found at one time or another in the puncture fluid. In one case it was found in two successive punctures, and in a third puncture it was absent and failed to give any culture when spread on media, and in a fourth puncture the diplococcus reappeared. To my mind this simply means that in the fluid obtained in the third puncture the diplococci were so few in numbers as to elude search conducted with the ordinary care.

The earliest period at which we found the diplococcus in cases of cerebrospinal meningitis of the epidemic type was within twenty-four hours after the onset of the disease, and we have established it as late as the fifteenth week of the disease. It is apt to elude search and fail to give any result on media in chronic cases of the posterior basic type especially.

In this connection the bacteriology of the fluids obtained from cases of tuberculous meningitis is of interest, and it may be said here that there has been much difference of opinion as to the presence of tubercle bacilli in fluid obtained by lumbar puncture in cases of tuberculous meningitis. Whereas Lichtheim, Lenhartz and Bernheim found that tubercle bacilli were constant in the sediment of the fluid obtained from tuberculous meningitis, others, such as Cassell and Marfan have asserted that their presence is only occasional. Our experience in this regard supports the contention of Pfaundler, that the discovery of tubercle bacilli in the fluid obtained by lumbar puncture in tuberculous cases depends

much on patience and technic. This is well seen in our own cases. At a time when our technic was imperfect, when we did not centrifuge our fluids carefully, we failed to find the tubercle bacilli. Of late, however, we have made a special study of this question, and during the past year, of 14 cases diagnosed clinically as tuberculous meningitis, tubercle bacilli were found in 13 by subsequent lumbar puncture. To my mind this would prove absolutely that tubercle bacilli can be found by careful search in the puncture fluid of all cases of tuberculous meningitis. In some cases the search must be quite prolonged. In some cases, especially of children brought in late in the disease, we failed to obtain tubercle bacilli in the puncture fluid before death; but they were found to exist in abundant numbers in the fluid obtained by puncture immediately after death. It is hard to account for this apparent inconsistency, but I explain it by the fact that there is during life probably a constant wave of motion in the cerebrospinal fluid, thus securing the equal distribution of the bacilli throughout the cerebrospinal space. As soon as death occurs this circulatory wave is suspended and a sedimentation occurs and the bacilli are obtained in the lower part of the canal.

Mortality. It need not be said here that in epidemics of cerebrospinal meningitis the mortality among children will vary largely not only with the severity of the epidemic, but with the malignancy of the infection. In some epidemics the malignant cases, that is, those that die within twenty-four or forty-eight hours, seem to be more numerous than in other epidemics.

Of 37 cases in five years' service previous to the present year, which clinically presented all the classic features of cerebrospinal meningitis, 21 were absolutely substantiated either by lumbar puncture or postmortem to be of the epidemic type. Of these 21 cases the mortality was 42.8 per cent. Of the whole number of 37 cases, some were not punctured because the symptoms were self-evident; others were punctured, but failed to yield but little fluid, with negative bacterial findings.

Most of the fatal cases occurred in infants below one year. Of 15 fatal cases, 8 were less than one year of age and 2 below two years. Thus, the older the child the better its chances of conquering the infection. I have records, however, of infants of five months and one one year of age who recovered and in whom the diagnosis of cerebrospinal meningitis of the epidemic type was substantiated by cultures from the fluid obtained by lumbar puncture.

COMPLICATIONS. In the 37 cases of epidemic cerebrospinal meningitis which form the basis of this paper we have noticed that the complications were exceedingly few. Those cases that recovered did so with very little to show that the nervous system in any of its extent had been severely compromised. The eyesight was not injured, nor was there in any of the cases a subsequent hydrocephalus. In other words, the recoveries, when they occurred, were complete and satisfactory. This is due not to any mode of treatment, I think, but only to the nature of the cases.

The most common complication seemed to be otitis. Herpes labialis was found in only 2 cases of the 37 and none of the cases presented joint complications, in this respect differing from the joint complications in the adult. I have lately seen 1 case of joint involvement. Erythemata and evanescent eruptions were observed here and there.

Most peculiar and striking have been several cases of the malignant type which I have seen this year in which death took place within twenty-four to forty-eight hours after the initial symptoms appeared. In both of these cases there was a scarlatinous erythema. This disappeared and was replaced by a purpuric eruption, extensive in character, the skin of the infants and children appearing as if they had been beaten. Ecchymoses were blotchy and of wide extent, distributed over the back, thorax, abdomen, and upper and lower extremities. The diagnosis in these cases left no question of a doubt, being substantiated by the presence of meningococcus in the fluid obtained by lumbar puncture.

POSTERIOR BASIC MENINGITIS. Still, of London, has given peculiar interest to this form of meningitis through his investigations of 15 cases of the disease. His clinical summary of the characteristics of these cases is quite classic, and may be mentioned here for the sake of completeness.

An infant becomes fretful, irritable, peevish, has one or more convulsions, vomits and then in a few days the mother notices that the head is drawn backward, the limbs are rigid and there is partial or complete opisthotonos. Quite a percentage of these cases last for weeks and may recover; others pass into the chronic stage, which may last for months, with complicating hydrocephalus. During the course of the disease the rigidity of the neck and retraction of the head become extreme, and finally the infant passes into a condition resembling a tetanic state, with its arched back,

its retracted occiput, the upper extremities in the position of extension, the hands clenched, very much as is seen in forms of tetany. The lower extremities remain in a condition of rigidity and of extension, and the feet and toes both extended. It was formerly thought that these cases were tuberculous; but Still has found that in 13 of his 15 cases he could isolate a diplococcus which to-day may be considered identical with the diplococcus meningitis. Still and Nuttall both consider this form of meningitis a type of sporadic cerebrospinal meningitis, with the same etiology as that of the epidemic cases. Anyone who has much to do with infants and children has seen these cases, and I have seen quite a number of them. These cases have come to me in the hospital in the subacute stage, and, as is very often the case, I have had no opportunity until recently to make a postmortem in a case of basic meningitis. In one case the fluid withdrawn by lumbar puncture was quite clear, resembling that of hydrocephalus. The fontanelle was bulging to a considerable extent, being open, and we drew off considerable fluid by repeated lumbar puncture. We have been unable, however, to cultivate the diplococcus meningitis from this fluid. The cytology in this case to which I refer showed a preponderance of mononuclear lymphocytes. In none of the cases have we been able to prove the tuberculous nature of the disease by the injection of cerebrospinal fluid into animals, and this, I am inclined to believe, would support the contention of Still that this type of cases is distinctly caused by the diplococcus meningitis, and is to be classed with the epidemic cases.

I have recently been fortunate in obtaining a postmortem on a case of posterior basic meningitis, in the puncture fluid of which I obtained the diplococcus intracellularis both by cover-glass stain and culture. The history of the case is as follows:

Female child, aged two years, with a negative family history. The child had been born normally, had not suffered from any infectious disease, although a year previous had an abscess in the neck, which was cured in three weeks. No history of ear trouble; has always been a healthy, bright child.

Present History. The illness was of five weeks' duration, began suddenly with fever and general convulsions; since then the child has felt better at times, and at other times, chiefly toward evening, the symptoms have reappeared. The child became stuporous since yesterday. The father thinks it is blind; it has vomited occa-

sionally for the past three days. There have been sudden movements of the upper and lower extremities. During this illness the child has become much emaciated. There is no cough. The bowels and urination are normal. No previous history of traumatism. The father has not noticed any enlargement of the child's head during the illness.

Present Status. The child lies with its head retracted and body slightly curved, the concavity somewhat to the left. There are occasional purposeless movements of all the four extremities, more marked on the right side. These are sometimes so limited as really to constitute tremors. The child starts at the least sound; is unconscious; the eyes are open, pupils dilated, though they react to light; the forearms are extended from the arms, the hands clenched; the lower extremities are extended, the feet extended, and the toes are flexed into the plantar surface of the foot. At times the child is rigid. There is rigidity at the back of the neck, and this rigidity is increased if the child is handled. At such times there is extreme opisthotonos; the head is drawn back at an angle to the trunk. In other words, there is a spastic condition of all the extremities. The knee-jerks are increased; there is no clonus. The spasm at times is extreme, and a good deal of force is necessary to move the hands or legs. There is a tache cérébrale. The respirations are very irregular, sometimes superficial, and at others deep. There is no paralysis either of the muscles of the face or those of the orbits of the eyes. The ears are negative; heart and lungs show nothing peculiar. The liver normal to percussion; spleen palpable just below the free border of the ribs. Abdomen retracted. The skin shows a slight erythematous rash on the trunk. The throat cannot be examined on account of the fixity of the lower jaw (trismus).

The further history of the case is uneventful. The temperature was normal on admission, rose toward the close to 101° The pulse ranged from 100 to 140, being quite irregular at times. The respirations ranged from 28 to 48. Toward the close the opisthotonos retraction of the head and rigidity became very marked. The child presented all the features that are characteristic of basic meningitis. The lumbar puncture was made in this case two days before the fatal issue, the child dying four days after admission to the hospital. A flocculent fluid was obtained which showed the presence of 73 per cent. polynuclear leukocytes and 27 per cent.

mononuclear lymphocytes. The spreads and culture of the puncture fluid showed the intracellular diplococcus negative to Gram. There was no sugar in the fluid. The child died suddenly in the afternoon of the fifth day after admission. A postmortem was obtained on the brain alone and showed a classic basic meningitis as described by Still, the exudate being abundant and purulent over the pons and crura. The convexity showed only slight meningitis; congestion was marked, and there were areas of opaque tissue in the pia of old organized foci of inflammation.

In the postmortems made by Still he found as an accidental complication recent or old tubercles in a few cases; but in these very cases he has been unable to find any tubercles of the brain or cord. On the contrary, he has established a diplococcus in the ventricular fluid and therefore considers the tubercles as an accidental complication and not a primary cause of the disease.

NOTE ON TREATMENT. The more we study the methods of treatment pursued in the management of cerebrospinal meningitis the more we are led to the conclusion that the disease, very much like pneumonia, is a self-limited one and that all we can do is to relieve the suffering of the patient and treat the complications. The results of methods of treatment seem to be very closely connected with the severity of the epidemic and that of the infection in the various epidemics. Thus, in an epidemic in Oporto there is a record of 56 deaths in 91 cases, a mortality of 62 per cent. In some epidemics the mortality has been quite low, 25 per cent., and in others higher than this percentage, as may be seen by referring to the section on mortality. And still in these epidemics very much the same treatment has been pursued, if we except one procedure, viz., that of lumbar puncture.

Much has been expected of lumbar puncture, and still it must be said, comparatively little has been realized from it in a therapeutic sense. Seager, in recording the mortality and treatment observed by him in cases of epidemic cerebrospinal meningitis, shows that by simple lumbar puncture 9 cases in 20 died, a mortality of 45 per cent. In the treatment by baths, 60 per cent. died. He then gives the statistics of the latest procedure, that of lumbar puncture, followed by the injection of a number of cubic centimeters of a 1 per cent. solution of lysol. Of 31 cases treated by such an injection into the cerebral spinal space, 13 died, a mortality of 42 per cent. In the same clinic where Seager observed these procedures

7 cases were treated with an injection of mercury oxycyanid, and 4 died. Neither of these procedures prevented relapses in the cases observed by Seager, and these were quite frequent. In the epidemic in Oporto 26 cases were treated by simple lumbar puncture. Of these, 8 died, a mortality of 30 per cent.

In considering the benefits of lumbar puncture in an epidemic of cerebrospinal meningitis there are some, such as Osler, Wentworth, Concetti, Travers, Smith and others, who think that this procedure is of decided benefit to the patient, inasmuch as headache and delirium are relieved. My own experience, and this is considerable, teaches me that we can only say that lumbar puncture is palliative rather than curative. Indeed, it cannot prevent relapses, as I have proven to my own satisfaction in cases in which the temperature had dropped after lumbar puncture, remained normal for a week, and then, without any apparent cause, a new attack was inaugurated. The fluid after the last puncture having been quite clear and sterile, possibly on account of the paucity of micro-organisms, became very turbid again, and there recurred an intermittent temperature curve, lasting over three weeks. I have seen the temperature rise after lumbar puncture, and the patient, on the surface, did not seem to have been benefited; but on a close study of the cases I found that the temperature is not a guide as to the efficacy of the procedure of lumbar puncture. Lumbar puncture certainly relieves symptoms of pressure, for in older children, who can describe their sensations, there is much relief after the withdrawal of 40 or 50 c.c. of fluid from the cerebrospinal canal. In fact, in one case, I remember distinctly a little patient of twelve who actually requested (so severe was the headache) that the procedure should be repeated, inasmuch as it was the only thing that gave her relief. Therefore, if the irritability is great and headache is severe, as may be judged even in children by the rational symptoms, lumbar puncture is indicated.

Again, if rigors are frequent, lumbar puncture is certainly indicated, inasmuch as a certain amount of purulent exudate is thus withdrawn in the same sense as it would be indicated in a pleurisy.

Lumbar puncture is inefficient in certain types of cases in which there is extreme retraction of the occiput, rigidity and even opisthotonos. In some of these cases introduction of a needle is attended by no results; that is, there is a dry tap. It has been shown that in these cases there is danger of sudden dilatation of the ventricle,

and what might have been relieved by the only procedure known in medicine, lumbar puncture, fails in the very cases in which it is most needed.

Again, lumbar puncture gives us a very good idea, in a prognostic sense, of the future fate of some cases. Where the cerebrospinal fluid is thick and purulent, and flows slowly from the cannula, the prognosis is grave. I have not succeeded in saving any of these cases. Particularly encouraging are the cases in which the fluid obtained by lumbar puncture is of a cloudy appearance, at most of a straw color.

In a procedure in which so little is known as to its efficacy, it is quite to be expected that all sorts of modifications should have been suggested. I refer to the injection of chemicals or antiseptic fluid, such as lysol and the oxycyanide of mercury.

Our treatment has consisted simply of a lumbar puncture whenever indicated by high temperature, continued excessive irritability of the patient, stupor, constant headache and delirium or rigors. Following out this method, we have felt that we had at our disposal a very excellent method, not only of relieving these symptoms, but of relieving pressure on vital organs, the brain and cord, at the same time withdrawing from the cerebrospinal space a certain amount of purulent fluid. In view of the fact that the bacterial life of the meningococcus seems to be a self-limited one, I doubt very much whether the procedure of lumbar puncture has a direct influence in shortening the disease. In younger infants and children, however, I do think that repeated lumbar puncture might aid materially in preventing certain complications, such as hydrocephalus following cerebrospinal meningitis, which is a very serious consequence with which to be confronted. Therefore, by relieving the pressure, we may possibly prevent in these young subjects a tendency which is present to dilatation of the ventricles and the accumulation of fluid therein.

Our experience with lumbar puncture has been quite extensive. We have never had an accident which could be attributed directly or indirectly to the procedure. Our method of performing lumbar puncture has followed closely that advised by Quincke. If we were unsuccessful and obtained what is known as a dry tap we have repeated the puncture in another space, but we have not gone farther than this. In several cases the primary puncture was followed by quite a profuse hemorrhage. Quincke thinks that this

hemorrhage can be traced to the puncture veins in the subdural space. In none of the cases in which hemorrhage occurred have we seen any ill effects follow. In fact, the cases in which hemorrhage occurred made a good recovery without paralysis of the lower extremities.

A peculiar symptom which I have not noted elsewhere is that of a desire to urinate at the time of the entry of the trocar in the cerebrospinal space. This, however, is only momentary, and disappears as soon as the trocar is withdrawn.

As to the number of times which a case should be punctured, there is, of course, no set rule. If the temperature remains down after a puncture, and the irritability is not very marked, nor the headache, it is well to hold our hand. If, however, there is a subsequent rise of temperature, accompanied by headache or delirium, we may puncture, though certainly not more often than at intervals of four or five days.

As to the quantity of fluid withdrawn in every case, this will vary. In some cases the fluid flows very rapidly from the cannula, is quite clear, or slightly turbid, and in a very short space of time 70 or 80 c.c. are withdrawn before there seems to be a relief of tension, which is judged principally by the rapidity with which the fluid flows from the cannula. If the fluid flows slowly, drop by drop, we rarely withdraw more than 30 c.c. at a sitting.

Our further treatment, as published elsewhere, consisted of hot baths for the rigors; sponging for the temperature; the intestinal canal was kept open with calomel, and we have administered in all of our cases potassium iodid and sodium in full doses.

I have never made a so-called cervical puncture; nor do I think that lumbar puncture can be ranked with aspiration of the chest as an emergency procedure. Thus, given a case of cerebrospinal meningitis with a very high pulse, such as has occurred in my practice lately of 200, a condition of coma and all the symptoms of malignant cerebrospinal meningitis, lumbar puncture has seemed of little avail as practised to-day.

A CASE OF MALIGNANT ADENOMA OF THE LIVER.

By GEORGE L. PEABODY, M.D.,
OF NEW YORK CITY.

Cases of malignant adenoma or adenocarcinoma of the liver have now been described in considerable number; but the condition is still sufficiently uncommon and in some of its relations sufficiently controversial to justify the recording of another. Indeed, as to nomenclature there is no agreement. Eggel,[1] calling all epithelial growths of malignant character carcinomata, includes these in that group; and clinically that would seem a useful designation. Morphologically, however, many of them are adenomata—as mine certainly is—and if we call them also "malignant" it would seem to me to describe them sufficiently.

History. The patient whose liver I show to-day was a Greek, aged thirty-eight years, a fruit dealer by occupation. He was admitted to the New York Hospital on October 5, 1903, and died a month later.

He spoke no language but Greek, and on this account his history was necessarily meager. Of his family history nothing was obtainable. He remembered no previous illnesses except gonorrhea two years before. He gave no history of syphilis. He admitted the drinking of beer, but denied indulgence in all other forms of alcohol.

He said that he had felt well until two weeks before admission, at which time his abdomen began to swell and he began to grow weak and short of breath. Apart from this he denied all symptoms. He had not been troubled by diarrhea, vomiting, headache, cough or pain of any kind; nor had he had bleeding from bowels or nose or mouth. His chief complaint related to his distended abdomen and the consequent shortness of breath and weakness.

On physical examination the following facts were noted: He was of small frame and poorly nourished. His skin and mucous membranes were of fairly

[1] Ziegler's Beiträge, Bd. xxx. p. 509.

normal color. His tongue was dry and coated in the middle. His pharynx and eyes appeared normal.

His heart was normal in position and rapid. There were no murmurs. Pulse was of fair size and force, with slightly increased tension. The radial and temporal arteries were somewhat thickened and the latter were also tortuous.

Percussion note was dull in both axillary regions low down. Behind it was flat from the angles of the scapulæ to the bases. The breath sounds were diminished in intensity at angles of scapulæ and gradually lost below these points. Vocal fremitus was absent over lower parts of both sides of chest behind. These signs of fluid in the pleural cavities subsequently disappeared. Elsewhere over lungs expiration was prolonged and a few wheezing rales were heard. His abdomen was tense and distended so that solid viscera could not be defined. There was movable dulness in the dependent regions.

Examination of his extremities revealed the knee-jerks present. There was distinct edema of feet and legs. Axillary glands were of the size of a large pea. Other superficial glands were not enlarged. Rectal examination was negative, prostate was not enlarged nor tender.

His urine was always of rather high gravity, from 1030 to 1034, of acid reaction; occasionally contained a trace of albumin, never any sugar, and occasionally a few granular casts. It was normal in quantity until the last week of his life, when it was passed involuntarily and could not be measured.

His leukocytes varied between 7800 and 12,500. The following differential counts of 300 leukocytes were made on the 13th and 19th of October respectively:

October 13th:			
Polynuclear neutrophiles	239	=	79 6 per cent.
Lymphocytes	47	=	15.6 "
Eosinophiles	9	=	3.0 "
Large mononuclears	5	=	1.6 "
Mast-cells	0		
October 19th:			
Polynuclear neutrophiles	238	=	79 3 per cent.
Lymphocytes	39	=	13.0 "
Eosinophiles	1	=	0.3 "
Large mononuclears	22	=	7.3 "
Mast-cells	0		

He had 70 per cent. of hemoglobin. His temperature was never high; a few times it was found as high as 100°, but generally it ranged in the neighborhood of 99° until toward the end of his life, when it was subnormal for several days. At death it was 94°.

His pulse fluctuated between 70 and 100, usually being between 80 and 90. It was usually soft and compressible. His respirations were occasionally somewhat accelerated, but usually about 20 or below.

He was much distressed by the size and weight and tenseness of his abdomen and was very wakeful. After the administration of saline purgatives for a few

days his abdomen was tapped. It measured in circumference at the umbilicus thirty-five and a quarter inches before tapping. On October 8th he was tapped and seven and a half quarts of very bloody serum were removed. Microscopically red blood-cells were extremely numerous, and a smear appeared like a fresh blood-smear. Red cells were normal in shape and size, not at all disintegrated, and were present in a cubic millimeter to the number of 697,600. After the tapping he was much relieved, and it then became possible to examine his abdomen by percussion and palpation as had not been the case before. His liver was found to be very small, its area of flatness extending only over the fourth space and fifth rib. Its edge could not be felt. The spleen could not be felt, but it percussed large. No masses could be felt through the soft, relaxed abdominal wall. After the tapping his abdomen measured thirty-one inches.

In spite of the fact that there was a constant leakage from the wound in the abdominal wall for the following three days, the fluid rapidly reaccumulated. The relief afforded by the tapping was marked, however. He slept well, as he had not done at all before. In four days his abdomen had regained most of its former size, and he was again oppressed by its weight and interference with respiration. His face began to show emaciation, and soon this was very distinct also in his body and limbs. He continued steadily losing flesh and strength; and gradually growing indifferent and stupid, without pain and without complaint, he died exhausted on November 6th at 9.15 A.M., one month after entering the hospital.

Autopsy. The autopsy was made the day after his death at 4.30 P.M. by Dr. George P. Biggs, the pathologist of the hospital. The body was much emaciated; rigor mortis was present; the upper part of the chest was narrow and prominent anteriorly; the lower part of the chest and abdomen were broad and full. There were no external evidences of syphilis.

Peritoneum. There were no adhesions. It contained three and a half liters of very bloody fluid, with no fibrous exudate. Investigation showed the source of this hemorrhage to be an irregular, nodular mass about 7 cm. in diameter, projecting from the superior surface of the right lobe of liver and about 7 cm. in diameter.

Diaphragm was on a level with the fourth rib on the right side and with the fifth rib on the left side. The network of veins on the diaphragm and in upper abdomen generally was enlarged and engorged.

Pleuræ were normal.

Pericardium was normal.

Heart was smaller than normal and weighed 225 grams. Its muscle was brownish-red in color; its valves and coronary arteries were normal.

Lungs. The bronchi were hyperemic and contained bloody fluid. Bronchial lymph nodes were enlarged and slightly pigmented. Both lungs were hyperemic, especially in the posterior portions, which were also the site of several areas of hemorrhage, varying in diameter from 1 to 3 cm. These had the

typical appearance of infarcts. The central portions of the larger of these areas were very firm and of grayish-red color. Obstructions could not be demonstrated in the vessels of these areas.

Spleen was very much enlarged and weighed 570 grams. Its capsule was moderately thickened, its consistence firm, its color normal. Its cut surface showed some increase of stroma.

Kidneys were slightly enlarged; their capsules were not adherent, surfaces smooth, cortices slightly increased in thickness, markings somewhat obscured. Both organs were hyperemic throughout. Pelves and ureters were normal.

Pancreas was normal in size and appeared to be normal in structure, but its tail was unusually firm.

Suprarenal glands were normal.

Stomach was markedly hyperemic. The mucosa was moderately thickened and coated with mucus.

Intestines were hyperemic throughout, but showed no other change.

Bladder was normal.

Prostate was normal.

Aorta was normal.

Vena cava inferior was dilated below its union with hepatic veins.

Hepatic Veins. The mouth of one of the main veins contained a soft, grayish-yellow, villous-like mass, which projected into the vena cava as a nodule one and a half centimeters in diameter, but did not entirely occlude the vein.

Splenic vein was thrombosed from the tail of pancreas to its junction with the mesenteric vein. The thrombus was firm and gray in its distal part and softer and redder in its proximal part.

Lymph nodes were normal except that those in the region of the lesser omentum were slightly hyperplastic. There was no appearance to suggest the presence of tumor-tissue in them.

Gall-bladder and large bile-ducts were normal.

Liver was much reduced in size and greatly altered in shape. The left lobe was very small and largely drawn behind the right lobe. The extreme measurements of the organ were 15 cm. vertically, 14 cm. transversely, and 10 cm. anteroposteriorly. This reduction in size seemed to be due to a very marked atrophic cirrhosis, which would appear to be at all events in part of syphilitic character from the numerous deep cicatricial contractions upon its surface. There is no quadrate lobe, nor is there any trace of it. These cicatrices explain much of the irregularity of the liver's shape, but this is due in part to extensive growth of tumor-tissue, the most prominent part of which is that seen on superior surface of right lobe, measuring 7 x 7 cm. and having an elevation of 5 cm.

The next most noticeable mass of tumor-tissue is in central portion of anterior surface of right lobe, where it measures about 8 cm. in diameter and projects above the surface to an uneven height of between 1 and 1½ cm.

Much tumor tissue is seen elsewhere throughout liver in masses of varying

size, constituting nearly one-third of its bulk, but it shows *upon the surface* in but very few small areas aside from the two large masses described. The large mass seen on the superior surface has grown far beyond the plane of the organ's surface, and in its left portion it showed when fresh a mass of coagulated blood which marked very plainly the site of the origin of the blood which had been found in the peritoneum both before and after death. The projecting parts of tumor were seen to be covered by Glisson's capsule, beneath which it doubtless originated in the substance of the liver. This capsule, which is generally moderately thick and continuous, is very thin and shreddy over the most prominent portion of the tumor; and at the site of hemorrhage there is seen in it a large, irregular rent, which had allowed the escape of blood. Tumor-tissue beneath this rent presents a ragged and hemorrhagic surface. Adjacent to this both omentum and diaphragm were firmly united to the covering of tumor by old fibrous adhesions.

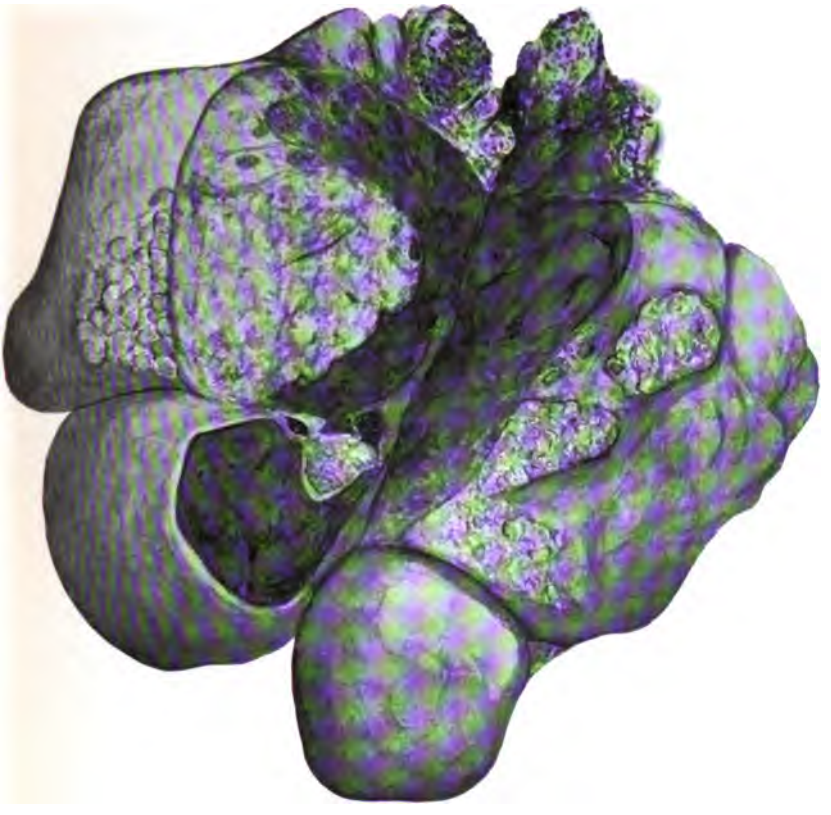
In many parts of liver the growth of tumor can be demonstrated within veins, and in one of the main branches of portal vein is seen a growth of tumor-tissue similar to that described as being in one of the large hepatic veins. When fresh the tumor-tissue was soft and its color was light yellow with greenish areas scattered through it. The liver-tissue was dark green in color and its lobules were not distinct.

Microscopic Appearances. Liver. The liver shows in sections everywhere very extensive development of connective tissue surrounding the acini. In this is seen very abundant proliferation of bile-ducts, which appear in the sections cut transversely, obliquely and longitudinally. In many places they have a distinct lumen. About the centers of the acini there is marked congestion and much pigment occurs in the zone surrounding the central vessels.

The connective tissue is seen in places to contain many aggregations of young cells; in others it is fully formed, dense and without many cells or nuclei. In general the cirrhosis is of the interlobular variety, but there are many wide bands of connective tissue which extend between many acini longitudinally. The formation of bile-ducts is much more extensive in some parts of the connective tissue than in others.

Tumors. The tumors present the tubular or trabecular variety of adenoma very generally. In many places the lumen is distinct, in others it is barely indicated and in others it cannot be made out. It does not contain bile anywhere. In older parts the structure is trabecular rather than tubular. In all the tumor-masses (and the liver-sections show many of all sizes from minute points to whole fields) many fat vacuoles are seen. There is but little stroma as a rule between the tubules. Dense bands of connective tissue occur here and there, separating large tracts of tumor-tissue from each other.

The tumor-cells are modified liver-cells, all bearing a general resemblance to liver-cells. They are usually larger than the liver-cells and their nuclei are often larger than those of liver-cells. They often contain two or more nuclei. The



Malignant adenoma of liver. New-growth seen in portal and hepatic veins.

cells vary very much in size and in shape. Caseous areas are occasionally seen. In some of these an indication of a general glandular arrangement can be made out with the fat vacuoles as seen elsewhere in the tumor, but without any definition of individual cells or nuclei, and with only a few connective-tissue nuclei visible in the not very abundant stroma. Besides the numerous small tumor-masses of microscopic size which are seen scattered through the liver-tissue, occasionally similar microscopic masses of similar formation are seen in the dense connective tissue between the acini. This would suggest that the cirrhosis was primary and the adenoma secondary in this case, although not certainly so. However minute these little islands of tumor-tissue are, their general arrangement of cells and fat vacuoles is exactly like those of the larger masses. This vacuolation is not seen anywhere in the liver tissue.

Similar microscopic masses of liver-tissue are also seen occasionally as little islands in dense fibrous stroma, and present a very different appearance from the tumor-islands in their arrangement and size of cells and in the presence of pigment. Pigment is nowhere seen in the tumor masses. Within small blood-vessels occasionally tumor-tissue is seen completely filling them. Actual transition from liver-tissue to tumor-tissue is nowhere seen, although in places liver-cords seem to be very nearly continuous with tumor-tubules. Everywhere, however, careful focusing shows that they are separated by connective tissue, which is sometimes very fine and delicate. No metastatic growths are found in other organs, although it is possible that microscopic metastases escaped my observation. Sections of masses found in hepatic and portal veins showed them to consist of tissue exactly similar to the tumor-tissue found in the liver.

Other Organs. What appeared to be a thrombus in the splenic vein proved actually to be that; no tumor-tissue was found in it. Examination of hemorrhagic areas in lungs, bronchial lymph-nodes, and omental lymph-nodes were all also negative as to the presence of tumor-tissue.

Kidneys showed chiefly thickening of the stroma in cortices.

Pancreas was normal.

Suprarenal bodies were normal.

The literature of this subject has been carefully collated, especially by Van Heukelom[1] and later and more fully by Eggel,[2] who, however, includes other kinds of malignant tumors, notably all primary liver carcinomata, irrespective of their origin. Some of his cases started in the gall-bladder, some in the bile-ducts. He calls all the tumors *carcinomata* because they all fall within his definition by being epithelial growths and malignant. His inclusion in his list of other tumors than those which I have described

[1] Ziegler's Beiträge, Bd. xvi. p. 341.

[2] Ibid., Bd. xxx. p. 506.

brings his total up to 163, of which only 85.4 per cent. show the coincidence of cirrhosis.

One of the most satisfactorily worked out of all the published cases is that by Catherine H. Travis in the *Johns Hopkins Bulletin* for May, 1902, p. 108. Her microscopic work is especially good. Her case and mine are the only ones that I have found in which profuse hemorrhage occurred into the peritoneum.

Marchwald[1] has studied 11 similar cases. He regards the connective-tissue growth as being always secondary to the tumors and not causative of them. The relation between the tumors and the atrophic or annular cirrhosis which have been found associated so commonly in these cases has been much discussed by Marchwald and others. It is still unsolved. Many writers regard the new growth as compensatory to replace destroyed liver-parenchyma; if this view be adopted it is, of course, quite unexplained why these neoplasms should not occur oftener in atrophic cirrhosis.

H. Fraser[2] describes a very typical case. Indeed there is an absolute identity in the details of many of the described cases. He also regards the new-growth as compensatory. Van Heukelom[3] tabulates 31 cases from other writers and adds 3 of his own from Rosenstein's clinic at Leiden. He carefully excludes all but those similar to the group that we are discussing, and he calls them adenocarcinomata. In all of the 33 atrophic cirrhosis was present.

Van Heukelom's[4] summary of the important facts in these cases is very apt. He finds the livers of very different sizes, rarely as large as they become in secondary cancers, rarely quite as small as in well-developed annular cirrhosis, although the bulk of tumor-tissue is often large and the cirrhosis can be far advanced. The liver is generally bile-stained and contains countless tumors, which are individually for the most part small. Their color is generally grayish or yellow or dark green. These growths may be very unevenly distributed through the organ, and then the left lobe is apt to be more extensively invaded than the right. In my case the right lobe was the site of chief invasion of the new-growth. The gall-ducts are not dilated and the blood supply is usually not great. The liver shows a very generally distributed cirrhosis, which is equally well pronounced in regions where there are no tumors.

[1] Virchow's Archiv, 1896, Bd. cxliv., 1, p. 29.
[2] Ibid., Bd. clxv., and Fortschritte d. Med., 1902, Bd. xx., No. 5, p. 174.
[3] Ziegler's Beiträge, Bd. xvi. p. 348.
[4] Ibid., p. 345.

In this latter respect it is in striking contrast with the distribution of the connective tissue in livers the seat of secondary carcinomata, in which it is limited to the proximity of the new-growths.

The form of the adenoma is trabecular or tubular, at least in its early stages; the cirrhosis is annular. The extent to which newly formed bile-ducts occur in the connective tissue is variable. The origin of the new-growth in bile-ducts is maintained by but few writers, whereas the development of its cells from liver-cells can often be seen. Metastasis in other organs is rare, but does occur. On the other hand both portal and hepatic veins are frequently invaded by the new-growth—a condition which he graphically describes as "carcinomatous thrombi." As far as clinical data allow a generalization he finds the liver adenoma with cirrhosis almost only among men. In this respect his experience is different from that of Marchwald,[1] who finds it in both sexes and at all ages. Van Heukelom finds it only in men about forty years of age, rarely much older.

The course of the disease, from the earliest complaint to the end, covers usually a period only of months. Ascites almost always occurs, jaundice usually. The diagnosis is rarely possible. In some cases where the liver becomes palpable after tapping it might be suspected, and in a few the presence of a tumor might be made out. It would be likely to suggest the probability of a secondary carcinoma under these circumstances during life.

[1] Loc. cit.

ADDISON'S DISEASE WITH AND WITHOUT ADRENAL TUBERCULOSIS.

By CHARLES F. WITHINGTON, M.D.,
OF BOSTON.

I AM well aware of the strong protest which the above title would have called forth from certain prominent medical writers of two decades ago, and which may still be made by some writers of our own time who, like their predecessors, hold to the so-called "unity" of this disease. This belief rejects from the category of Addison's disease all cases in which the pathologic lesion is aught else but a tuberculosis of the adrenal glands. For example, Greenhow[1] in his admirable Croonian lectures of 1895, in which he studies 330 cases thus diagnosticated, accepts only 103 as perfectly typic, because in only that number were there found tuberculosis of the adrenals without any organic disease of any sort outside of these glands. To these he adds, with reservations, 80 more, 16 as being probably incompletely reported in certain details and 64 others which, while showing the full clinical picture of Addison's disease, did have lesions outside of the tuberculosis of the adrenals which lesions gave rise, in his opinion, in many cases to symptoms of their own and in a few instances modified or obscured some of the usual symptoms of Addison's disease. Two of the groups which Greenhow rejected were thrown out because of the lack of complete conformity to the Addison complex, in that in one case there was no disease of the adrenals and in the other group a non-tuberculous disease was found.

Certainly, the rejection of cases of Addison's complex arising from cancer of the adrenals, because the disease was not tuberculous, is hardly to be taken as proof that Addison's disease can never arise except from adrenal tuberculosis.

Wilks was also an adherent of this view of the unity of Addison's disease, though it is to be remembered that Addison[2] himself was of the opinion that not only one fibrocaseous lesion, but others, such as cancer, might produce the symptoms.

Dr. Dyce Duckworth[3] expresses his general adherence to what he calls the doctrine of Guy's Hospital school, that the lesion of this disease is a specific and tuberculous one, and says, "It appears probable that continued research into the nature of the specific deposit and changes met with in Addison's disease of the adrenals will render it certain that these changes are always of a tuberculous nature."

Yet, despite this dogmatic statement, he admits some of the difficulties in the way of the simple unity of the disease, and more than hints that a broader pathogenesis may have to be sought for it.

Now, the term Addison's disease is to be considered to indicate a clinical syndrome, consisting of bronzed skin, constitutional disturbance, gastrointestinal irritation, and usually progressive weakness.

The bronzing is the most conspicuous feature, but not the solely essential one. It has been said to be an indirect rather than a direct adrenal symptom. It may even be absent, though if so the disease can hardly be diagnosticated antemortem. As has been said, the bronzing bears somewhat the same relation to the rest of the disease that the eruption of scarlet fever does to the other manifestations of that disease. Both the bronzing and the rash may be absent, though very exceptionally. But the eruption alone is not scarlet fever, nor is the bronzing Addison's disease. Each, plus its own allied symptom-group, warrants the respective diagnosis.

With this very proper precaution as to diagnosis, Addison's complex is certainly observed in more than one sort of pathologic process.

Admittedly the great majority of cases are found in tuberculosis of the adrenals.

But Lewin's[4] well-known figures are to be borne in mind. Among 281 cases he found: typic cases of Addison's disease with sound adrenals, 20 per cent.; typic cases of Addison's disease with diseased adrenals, 80 per cent.; disease of adrenals without bronzing, 28 per cent.; disease of adrenals with bronzing, 72 per cent.

Let us, then, in the present study adopt the following classification:

I. Cases with skin bronzing.
   A. Adrenal tuberculosis, the commonest type of Addison's disease.
   B. Adrenal disease, non-tubercular:
      Atrophy.
      Chronic interstitial inflammation.
      Cancer.
      Occlusion of adrenal vein.
      Hemorrhages.
   C. No adrenal disease:
      1. With disease of the semilunar ganglion.
      2. Without disease of the semilunar ganglion.
      3. Pigmentation, usually without other symptoms of Addison's disease.

II. Cases without skin bronzing.
   A. Adrenal tuberculosis:
      1. With tuberculosis elsewhere.
      2. Without tuberculosis elsewhere.
   B. Adrenal disease, non-tubercular:
      1. Cancer.
      2. Tumors.
      3. Necrosis, etc.

The cases of Addison's disease which I have to report, and which are limited to such as have postmortem evidence to sustain them, fall under the first two of the above categories. Three of them correspond to the commonest type, showing well-marked adrenal tuberculosis, with small amount of tuberculosis elsewhere in the body. The fourth case is of greater interest, as being clearly one in which there was absolutely no tuberculosis of the adrenals, but a simple and extreme atrophy.

Case I.—Mr. H. S., aged forty years, seen in November, 1897, with Dr. Clement, of Roxbury, to whose courtesy I am indebted for the history.

Patient, male, aged forty years, had always enjoyed good health. Several years ago had a severe injury to the foot, followed by inflammation and suppuration through the sole. Always had a dark complexion, but for a year past had been growing darker, as observed by his friends. Dr. Clement was called to see him the last of February, 1897, at which time he complained of great weakness, loss of appetite, nausea and vomiting. About a year before this he began to lose flesh and strength; at times was faint and nauseated, particularly

on moving or rising. During the summer he was quite miserable, but went away and improved, gaining ten pounds in weight. After returning in the autumn he said he "felt quite well." Four weeks after that he began to fail rapidly, though he continued to work to within three weeks of his death. Never had a cough. Skin pigmentation began about this time. The skin was a quite uniform mahogany color over most of the body, and there were dark patches on the mucous membrane of the mouth. The skin was that of a dark mulatto, the hands and face being the darkest part. No mottling of the skin, but a uniformly deep mahogany color. His emaciation was not extreme. He lived about a week after first calling medical aid, the nausea and vomiting continuing until exhaustion caused his death. His mind was clear to the last, long after his pulse at the wrist had ceased.

At autopsy both pleural cavities were obliterated by adhesions with a few small, hardened, tuberculous areas at apex of lung. There were no other evidences of tuberculous disease than in the lung apices and the adrenal glands. These were removed with the kidneys, and Dr. W. T. Councilman kindly examined them, and reported as follows:

"Two kidneys and a portion of apex of lung brought for examination. At the apex of the lung there are circumscribed, dark pigmented, radiating, cicatricial areas and about these various small, miliary, caseous foci.

"Both kidneys and adrenals present. The right adrenal is firmly adherent to liver. The gland enlarged; on section showed a central area of caseation with partial puriform softening, and around this dense cicatricial tissue in which miliary foci can be seen. The fat is apparently hyperemic and extends into the tissue.

"None of the adrenal tissue, as such, can be made out. In the kidney immediately bordering this the cortex is white, swollen, somewhat softened, and in the cortex at one point there is an obvious extension of the process. At this place no separation can be seen between the adrenal tissue and that of the kidney. Elsewhere there is no lesion in the kidney. The left adrenal gland easily separated from the kidney. It is reduced to the size of a filbert, and in this there are caseous areas and cicatricial masses. There is no evidence in either adrenal of any remains of the glandular structure."

Case II.—A. A., male, single, aged thirty-five years, Syrian, peddler, entered Boston City Hospital February 20, 1903. History of some illness two years ago, with cough, vomiting and fever. Says he made complete recovery. Worked until three weeks ago, then chilly, slight cough, headache, backache (which last he ascribed to carrying heavy bundles).

Patient is undersized, not well developed. Temperature, 102°; pulse, 104; respirations, 28. Skin throughout the body is very swarthy, evenly. This color was supposed to be a racial peculiarity. The patient spoke little English and no friend visited him. Nothing could be learned as to any recent increase of pigmentation. Pupils were equal and reacted well. No hemiplegia; tongue protruded straight. Respiration over both apices in front is harsh, without rales.

Over both bases behind equally subdued, without rales. The examination was otherwise negative, save for a markedly scaphoid abdomen. Kernig's sign present; no Babinski. Patellar reflexes equal and present. Attempted extension of left leg causes pain in lower lumbar region. Leukocytes, 16,400. The following day there was only slight patellar reflex; some rigidity of lumbar muscles.

February 23d there was great restlessness, with some vomiting. Lumbar puncture was done, and 50 c.c. of slightly flocculent fluid withdrawn, some tension within the canal being shown. This fluid proved to be sterile. The patient became drowsy; there was considerable retraction of the head, with flexion of the lower extremities; he died on the 24th, two days after admission.

The autopsy showed adherence of right pleura at base and both apices. Few small, old tubercles at both apices. No tubercles were found in brain or meninges. There was chronic fibrous thickening around the veins of the sulci. Vessels of the base were normal. The lateral ventricles and the fourth ventricle contained an increased amount of clear, straw-colored fluid. The pia, especially over the cortex, contained many scattered pigment spots, which were thought to be due to diffused modified hemoglobin. There was no evidence of intracellular pigment beyond a moderate number of the pigment and detritus-containing phagocytes so frequent in this region. A small ischiorectal abscess was present.

The left adrenal was a large, tuberculous mass, 5 cm. by 2 cm., varying from calcareous to puriform in constitution. Right, similar but not so large; size, 2 cm. by 3 cm. The diagnosis of Addison's disease was not made in this case during life, but the constitutional symptoms and swarthy color of the skin, taken in connection with the findings of the autopsy, warrant the diagnosis.

The absence of demonstrable tubercles in the meninges was, in view of the clinical symptoms and of the hydrocephalus, a surprise. The presence of considerable pigmentation on the pia is interesting in view of the statement of Duckworth, that it is doubtful if pigment is ever found deposited in any internal organs in Addison's disease, though he quotes one observation by Carrington of pigment in the pia mater.

Case III.—Autopsy by Dr. F. B. Mallory, who kindly gives me notes of the case. Patient, a woman, aged thirty-three years, well built, fairly well nourished. The clinical symptoms had consisted of progressive weakness; the duration about a year. The attention of the physician had apparently not been attracted to the adrenals. Hair rather light in color; skin dark in color, like that of a brunette. Areola of nipples dark. Conjunctivæ slightly pigmented. Bronzing general. Gall-bladder and ducts normal. Bile flowed easily into duodenum. Pancreas, stomach and intestines apparently normal. Adrenals each contain a caseous mass less than 1 cm. in diameter. Besides this small areas of caseation and calcification. Thin, small masses of fibrous tissue. Both glands much dimin-

ished in size. No trace of adrenal tissue. Small, flattened, caseous nodules in semilunar ganglion. Several adjoining glands enlarged.

Anatomic Diagnosis. Chronic tuberculosis of adrenal glands, semilunar ganglion, and of adjoining lymph nodes.

CASE IV.—Adrenal atrophy with Addison's disease. I. E. P., female, aged thirty-five years, born in Germany; housework. Had measles, smallpox, chickenpox, and scarlet fever when young. Rheumatism at eighteen years. Has been well since. Patient states that pigmentation of skin has come in past year. Since last summer has been run down. Complains of pain in feet and ankles, extending up to knees. Feet have been swollen at times. At times has had dull pain in her hands. Gets out of breath easily. Gets up once at night to pass water. Eyesight not very good, especially in right eye. No cough. Appetite fair. Digestion is good. Bowels constipated. Chief complaint is weakness.

Physical Examination. Well developed; cachexia; pale. Face covered with irregular pigmented areas, varying in size from 1 mm. to 5 cm. in diameter, occupying old smallpox scars.

Abdomen. Not distended. Considerable voluntary spasm, so that palpation is difficult. No masses felt. Separation of recti.

Skin. Irregular pigmented areas scattered over entire cutaneous surfaces. Pigmentation most marked in axillæ, groins, abdomen and back.

March 2d. Liver edge just felt in full respiration. Movable kidney on right felt with great distinctness. Chest and heart negative. Marked diffuse brownish pigmentation back of neck, axillascapular regions. In lumbar region it is more markedly macular. Marked pigmentation at folds of knee-joints. Face is now marked with pigment in each cicatrix, which patient says was not present one year ago. Tuberculin test negative, but not to be considered, owing to unreliability of tuberculin used.

5th. Since admission has shown marked general weakness. Complains of general pains in shoulders and extremities. Nauseated and vomited on several occasions. Yesterday afternoon up in a chair for short time. No apparent change in condition noticed afterward. About 11 P.M. patient found in a state of collapse. Heart action slow and weak. Pulse (radial) barely felt. Extremities cold. Marked pallor; very much excited. Emotional, groaning and crying out persistently. Cries due to fright from weakness—not from pain. Failed to respond to stimulation, and died at 4.05 A.M.

Autopsy, thirty-two hours postmortem, by Drs. F. B. Mallory and R. L. Thompson. Body length 152 cm. Body of a slender, gracefully-built woman. Lividity of dependent parts. Pupils 6 mm., equal. Rigor mortis present. No edema. Over the face and neck are closely set brown macules, mostly discrete, 0.5 cm. to 1.5 cm. in diameter. There is a slight brownish tint to the skin over the abdomen and about the axillæ.

Peritoneal Cavity. Very little omentum or retroperitoneal fat. Serosa pale in color, normal in appearance. Right kidney lies directly under gall-bladder,

and is freely movable. Mesenteric lymph nodes slightly enlarged, grayish-red in color. Appendix 6 cm. long; retrocecal; has a mesentery to tip. Diaphragm extends to fourth space on left, fourth rib on right.

Pleural Cavity. There are a few fibrinous adhesions about the right apex. Remainder of cavity normal.

Lungs. Voluminous; show the usual carbon tracery. Posterior portions somewhat congested. At the right apex pleura is thickened, and there is an old fibrous nodule, 3 cm. in diameter, the center of which is filled with cheesy material surrounded by thick fibrous wall. The remainder of the lungs is dark red. On section considerable blood-stained fluid exudes on pressure. Bronchi contains sticky, mucoid material.

Kidneys. Weight, 230 grams. Cortex, 6 mm. Capsule strips readily, leaving smooth surface marked with stellate veins. On section kidney is pinkish-red in color. Cortex and pyramids show normal differentiation. Glomeruli seen as fine, glistening dots. Fresh section shows large amount of fat in small and medium-sized droplets in basement membrane of tubules.

Adrenals. Very small in size, both together weighing less than 5 grams. Medulla practically not to be made out. Right with considerable connective tissue weighs 2 grams; left, 2.25 grams.

Microscopic Examination of Adrenals. The lesions consist in atrophy of the gland with destruction of the adrenal cells, marked fibrous change and areas of lymphoid and plasma-cell infiltration. A greater part of the atrophied gland, both cortex and medulla, is replaced by fibrous tissue. Other portions show narrow areas, in which are remnants of gland tissue, detached from the basement membrane and in various degrees of degeneration. These detached cells lie in connective-tissue stroma, which is infiltrated with lymphoid and plasma cells. The lymphoid and plasma cells sometimes form definite focal areas in which may appear an occasional adrenal cell. Bloodvessels are injected, walls not thickened. No evidence of tuberculosis could be found in either adrenal.

ADRENAL ATROPHY. The case last reported belongs to a category, not large, of simple atrophy of the adrenals. As such cases are likely to be challenged by a believer in the "unity" of the disease I append a brief report of a few other cases.

Barlow[5] reports a case of a woman, aged forty-two years, in whom both the adrenals together weighed less than 0.5 drachm. There was also gumma of the left kidney. There was brown pigmentation, most marked on the neck, behind, and in both axillas, around the nipples, flanks, and groins, also in the mucous membrane of the mouth. The inner side of the knees and the dorsum of each foot showed an irregular mottling of darker pigmentation. The abdomen showed a dark line from pubes to ensiform. She had had a recent pregnancy, terminated by delivery of a stillborn child, but

the pigmentation had antedated the pregnancy and developed rapidly since its close. There was fever (99° to 102°), vomiting and death.

F. Roloff[6] reports a case in which there was characteristic Addison's disease in a man, aged twenty-two years, in whom this pigmentation had begun thirteen years before, but who had felt practically well until five days before his death. The postmortem revealed only an extreme atrophyof both adrenals without the slightest tuberculosis. There was also no lesion of the semilunar ganglion.

Philips[7] reports a very similar case, where pigmentation had begun fourteen years before death, but for seven years had been unaccompanied by any symptoms. The adrenals were atrophied, not tuberculous.

Both these writers have apparently independently made a collection of all similar cases from the literature, which together amount to fourteen. In all of these tuberculosis was absent from the adrenals and in only three was there tuberculosis of any part of the body; in two cases no adrenals were found. To these 14 cases of adrenal atrophy with Addison's disease the one above reported adds a fifteenth.

Rolleston[8] calls attention to the fact that the adrenals may diminish in size in old age, but in his 1050 postmortems found them small in only six patients under forty-five years of age. These showed no signs of Addison's disease. But he adds that he has never seen the extreme atrophy described in some cases of Addison's disease in which the organs were reduced to the size of peas.

Cancer of Adrenals. In his original paper Addison included 3 cases of secondary carcinoma of the adrenals, and one in which a secondary carcinomatous nodule blocked the adrenal vein and caused hemorrhage into the capsules. These he later wished to remove from the category, and ascribed their share in the production of the symptoms to the proximity of the lesions to the sympathetic.

Greenhow rejects 9 cases of Addison's disease with adrenal cancer, 6 as not being Addison's disease and 3 as (while undoubtedly Addison's disease) *not* cancer, but tuberculosis of the adrenals. One of these reported by Gage, of Worcester, occurred in a woman whose breast he had removed for scirrhus two years before without recurrence. There were pigmentation and constitutional symptoms for six months. The adrenals were joined together by a thickened mass of enlarged and diseased lymphatic glands. This case is

rejected on account of the lack of microscopic examination, but as many of the cases were before the days of the microscope and this test was not insisted on when the disease appeared to be tuberculous, the justice of this ground of exclusion does not appear.

Other writers like Rolleston do admit cancer as a possible cause of Addison's disease, though it is apparently rare and both glands may be destroyed by cancer without the production of symptoms. But the same is true of tuberculosis.

Hemorrhages into the substance of the adrenals have been noted as connected with Addison's disease, not only in the case reported by Addison himself and above referred to, but also by Virchow as seen in some rapidly progressing cases of Addison's disease.

I. ADDISON'S DISEASE, INCLUDING BRONZING AND CONSTITUTIONAL SYMPTOMS, WITHOUT DISEASE OF THE ADRENALS.

Lewin in his classic monographs finds, among a total of 281 cases, 68 patients with the symptom-complex, but without lesion of the adrenals, being something like 20 per cent. of the cases. Shall these be rejected because they do not conform pathologically to the more common type? Lewin sees no reason to reject them on this ground, although other authors are inclined to do so in similar cases.

Let us consider for a moment, as fairly illustrative of this class, the case of Merkel.[9] A man, aged forty-six years, ill-nourished, shows weakness, decrepitude, anorexia and a strikingly bronzed skin, including both the covered and uncovered parts of the body. Although he has always been dark, the pigmentation has greatly increased of late. He has dark spots on the buccal mucous membrane. Fever, vomiting, abdominal distress, diarrhea, increasing weakness, delirium, death. The antemortem diagnosis was Addison's disease, of which the buccal pigmentation (pointed out by Niemeyer as pathognomonic) seemed to the author the final and conclusive symptom. Postmortem there was moderate internal hydrocephalus, with granular ependyma, miliary tuberculosis of the peritoneum and of an enlarged spleen, perisplenitis, perihepatitis, scant miliary tuberculosis of the liver and fatty degeneration. Normal adrenals. Some enlarged retroperitoneal glands, but no caseous focus. The skin pigment was like that in Addison's disease, granular and distributed in the deep cells of the rete Malpighii.

Yet Merkel, on the strength of the autopsy, eliminates this case from the category of Addison's disease, saying merely that the case destroyed for him the pathognomonic significance of pigmentation of the mucous membranes in connection with the rest of the Addison complex.

Another case instructive in this connection is that of Richon.[10] A girl of ten years, whose father died of phthisis and whose three brothers and sisters had died young, had complained for two months of weakness, anorexia, was depressed and always sitting or lying down. There was a darkening of the skin on the face, brow, commissure of the lips, trunk, back, glands and buttocks. The backs of the hands were especially dark-chocolate colored; some darkening of the buccal mucous membrane. Consolidation of both apices. The injection of adrenal gland caused restlessness and vomiting, and was discontinued. She began to improve after three weeks and left the hospital much better. Returning after an absence of three and a half months, the pigment had gone from the face and was less on the rest of the body. In the middle of a month's stay in the hospital the pigmentation began to return. She again left the hospital, was taken with abdominal pain, vomiting and cough. She was in bed for three months with vomiting and diarrhea. At the end of that time she entered the hospital again with no vomiting, but with increase in pigmentation and prostration, which in two months proved fatal.

The postmortem showed no lesion of either adrenal, either tubercular or otherwise. There was tuberculosis at the apex of each lung. In the lower 40 cm. of the ileum there were ulcers with perforation. The semilunar ganglion and the ganglia of the solar plexus and the sympathetic nerves were all normal. They were surrounded but not pressed upon by voluminous lymphatic glands. Richon also quotes a case of Brault and Perruchet like his own case, except that theirs, while showing no lesion of the adrenals, did have a small tuberculous mass adherent to and penetrating the semilunar ganglion.

An important case is that of Jürgens,[11] which was that of the full Addison complex in a patient with a big aneurism of the aorta, which caused compression of both splanchnics and so atrophy and loss of function of both the corresponding adrenals. On the strength of this and another case, the author claims that in every case of true Addison's disease there is a gray degeneration of the nerve

fibers of the splanchnics. This may be either protopathic, when one finds simple atrophy of the adrenals without other inflammatory appearances in these or other organs, or (more commonly) deuteropathic, in consequence of primary disease of the adrenals or pancreas.

These changes of the sympathetic system of the spinal ganglia and even of the cord have been recorded by many observers, but, on the other hand, have been definitely excluded in a sufficient number of cases to show that they are not essential to the production of the symptoms in question. Neusser says that minor degrees of such degeneration are found in various cachexiæ like pulmonary tuberculosis, and hence are of no significance. Most writers agree with Mann[12] that the structural changes which are usually present in the adrenals may or may not be followed by secondary changes in the semilunar ganglion.

Let us not forget, as Jaccoud has said, that bronzing without progressive asthenia and without visceral disturbances is not Addison's disease. Thus we shall not be misled into accepting the large number of cases which are on record as "simulating" Addison's disease, chiefly by reason of extensive skin bronzing. Certain affections of the female genital apparatus produce such bronzing, varying in extent from the pigmentation of pregnancy through the common chloasma uterinum to the pigmentations connected with marked ovarian disease, like that reported by Neusser,[14] where there was marked cystic degeneration of both ovaries with much skin pigmentation, which disappeared after the removal of the ovaries. Other skin pigmentations, sometimes extensive, are observed in diseases where cachexia may heighten the resemblance to Addison's disease. Still they are generally bronzing *plus* cachexia, not bronzing *with* cachexia. Such phenomena have been reported in scurvy; in chronic tuberculosis, especially of the peritoneum; in cirrhosis, particularly in Hanot's hypertrophic cirrhosis with diabetes;[13] certain pancreatic affections, with and without diabetes; in old amyloid disease; in chronic splenic enlargement with and without chronic malarial poisoning; in pellagra; in "vagabond's" disease; in chronic rheumatoid arthritis; in exophthalmic goiter.

II. TUBERCULOUS AND OTHER LESIONS OF THE ADRENALS WITHOUT ADDISON'S DISEASE.

The records of the Boston City Hospital show the following cases of adrenal tuberculosis without bronzed skin:

CASE V.—(I. Medical.) S. W., female, aged twenty-seven years, single; housework; rheumatism three years ago. Two weeks ago gave up work, tired out, weak, pain in right ankle; temperature, 102°; pain and tenderness of joints with fever continued. Nothing detected in the lungs. She died after six days.

There was stenosis and insufficiency of mitral valve and an acute endocarditis involving mitral and aortic valves. Passive congestion of the lungs. Old tuberculosis of old apices with miliary tubercles about them. Both adrenals enlarged; in both firm, completely caseous areas, surrounded by some dense tissue, a small portion of gland substance remaining in each. No record in clinical or autopsy notes of bronzed skin.

CASE VI.—May 26, 1902. (II. Medical.) S. D., aged nineteen years, single; elevator boy. Malaria two or three times. Typhoid years ago. For three weeks "tired out," abdominal pain, diarrhea. Consolidation left base behind. Temperature, 102° to 103°. Bowels continued distended, but patient rather more comfortable. After nearly two months temperature still up. Prolonged expiration and crackling rales throughout right chest; friction, right axilla; few dry rales, left chest. Abdominal examination negative. Tubercle bacilli present.

July 24th. Sharp pain in left side; friction rub.

28th. Intestinal hemorrhage; spasm right rectus muscle, tenderness right of and below umbilicus. Spasm and pain intense. Pulse 140; temperature normal.

These conditions, with increased abdominal distention continuing, he was transferred to surgical side for operation, which was performed August 2d. There was found intestinal tuberculosis, with perforation. Fistula persisted, and he died August 8th.

At *autopsy* there was found chronic tuberculosis of right apex; tuberculosis of mesenteric lymph nodes with softening; peritonitis; disseminated tuberculosis of lungs, spleen and liver; tuberculosis of adrenal and bile-duct. The left adrenal was enlarged, particularly in the middle portion. On section inner and outer edges of adrenal appear normal, but interposed between these two is a firm, yellowish-opaque mass, granular on section, sharply circumscribed and roundly contoured, which occupies the middle portion of the adrenal. In this area no traces of adrenal structure can be made out. It is impossible to demonstrate gross continuity between this adrenal and a large tuberculous lymph node in its proximity. The right adrenal does not appear to have been affected. No skin pigmentation.

CASE VII.—T. M. (II. Medical.) This case, adult male, pathologically showed nothing but a general lymphomatosis, with persistence of thymus and of red marrow. There was no tuberculosis demonstrated except in the right adrenal, which was firmly attached to the right kidney in a fibrous capsule, looking something like an elongated node. On section the upper part shows characteristic pigmentation of adrenal, but lower two-thirds for a distance of 3 cm. shows on

section an opaque, yellowish induration which completely obscures adrenal structure. A node embraced in the same capsule with the adrenal shows similar yellowish center, which has advanced to a trace of caseation. No skin pigmentation present.

Other cases of extensive adrenal tuberculosis without Addison's symptoms are not wanting. For instance, Rolleston found in his 1050 postmortems 18 cases where there was caseation in the adrenals (11 unilateral and 7 bilateral) without evidence of Addison's disease.

Lewin found 53 cases where the adrenals were tubercular without skin bronzing.

Roloff narrates a case of total bilateral tubercular inflammation of the adrenals without bronzing.

That in such cases as the foregoing a certain amount of adrenal function is still possible, through the existence of "adrenal rests," or accessory adrenals, is entirely possible. These adrenal rests may be found not only in the loose connective tissue, but embedded in the kidney or liver. Rolleston found five of these of the size of grains of corn on one side in one case where the adrenal was caseated.

Of other adrenal lesions without skin bronzing the Boston City Hospital records afford several cases. For example, there are three of cancer, as follows:

One of the cases was found in a patient dead with pneumonia and gangrene of the middle and lower lobes. Carcinoma was not diagnosticated during life, but was found postmortem in the liver, with metastasis in the omentum, mesentery, pleural surface, retroperitoneal glands and left adrenal gland. There was a healed tuberculosis of the left lung, but no skin pigmentation.

The other adrenal carcinoma was in a patient dying with palpable tumor of the stomach, with carcinoma demonstrated postmortem in the stomach, and with metastasis in the liver, lymph glands, rectum and adrenal. No pigmentation.

In another case where the surgical diagnosis was intestinal obstruction there was carcinoma of the cervix, with extensive metastasis, including the adrenals. No pigmentation.

There were two cases of atrophy—one in a patient dead of operation for ablation of the Gasserian ganglion for facial neuralgia. Pancreas and adrenals were all atrophied. No skin symptoms.

A similar atrophy of both adrenals and pancreas was found in a patient dead of organic disease of the heart, with dyspnea, edema, etc., but without skin pigmentation.

Four cases classified as "adrenal tumors" were apparently all of the same structure as the gland itself. One was a small tumor found in a man with fractured rib and lacerated liver. A second was in a man dead with chronic and acute pulmonary tuberculosis. The autopsy showed tuberculosis to exist also in the intestine, the peritoneum, and there was hyperplasia of the bronchial lymph nodes. Slight chronic peritonitis. The adrenals were normal in size. In the right one was a small nodule, size of a pea, in the substance of the gland, yellowish white, paler than the cortex to which it is connected, homogeneous, contour sharply marked. The left adrenal has a small cyst (5 mm.), irregular contour and containing a small amount of brownish fluid material. Microscopically this shows cells like the cortex. Despite the extensive tuberculosis elsewhere, these tumors of both adrenals do not appear to have been of that character. The patient had presented marked cyanosis, but no skin pigmentation.

A third tumor was found in the left adrenal, having the dimensions of 2 x 1.5 x 1.2 cm. It was composed of yellowish tissue like the cortex. The right was normal. The patient had died "uremic," with amyloid kidney, aneurysm of the aorta and obliteration of the pulmonary artery. No skin pigmentation.

A fourth tumor was larger, occupying the right adrenal gland, which measured 6 x 5 x 3 cm. It was yellow and firm, size of a walnut, yellowish-gray, capsulated. Does not thread out. Blood content low. The patient died of chronic bronchitis. No skin pigmentation.

A case of necrosis of the left adrenal was found in a patient with pancreatitis and is chiefly interesting from its pathologic features other than those connected with the adrenals.

The patient, a woman aged forty-nine years, had acute abdominal symptoms, with a somewhat vague tumor in the site of the left kidney, which it was thought might be a pyonephrosis. Operation disclosed a brownish-black, soft, pliable mass the size of a small orange, posterior, inferior and lateral to the left kidney. The kidney was normal in size, color and consistency, with no distention of the ureter. Fat-necrosis was found. The mass was removed and the cavity drained. The patient survived nearly ten days. The autopsy showed necrosis of the pancreas. Wirsung's duct patent. No stones. The gall-bladder ducts were empty and patent, the common duct dilated and two mulberry stones smaller than cherries were found in the gall-bladder. The necrosis involved, besides the body and chief part of the head of the pancreas and the left perinephritic region, the left adrenal gland. No skin pigmentation.

That the tuberculous element in the adrenals, however frequently it is found, is not the sole and essential cause of the Addison complex is suggested by the experiments of Vecchi,[15] who injected tuberculous bacilli into the adrenal glands of rabbits. A tuberculosis of these glands was produced and there was extension of the process to the central nervous system, but no pigmentation either of the skin or mucous membranes was produced. He believes that these symptoms of Addison's disease are the result of two factors, adrenal insufficiency and an intoxication produced by the tuberculous process. But if the tuberculous process is, as we have shown, not an indispensable part of the disease, why should we not return to what was practically Addison's own theory, that any disease involving adrenal inadequacy may produce the symptoms, and that the part played by tuberculosis is simply that it happens to be the most frequent destructive lesion of the adrenals?

In 1885 Hadden[16] noticed the similarity of lesion in his case of Addison's complex from interstitial atrophy of the adrenal to the lesion existing in the thyroid in myxedema. Osler[17] pointed out more in detail the analogies between the loss of an internal secretion, as producing in the case of the thyroid myxedema, and in the case of the adrenals, Addison's complex. It is interesting in this connection to note that Rolleston in 1896 had suggested that in certain cases of adenomata or hyperplastic tumors of the adrenals the symptoms might be due to altered structure and depraved secretion, just as Graves' disease depended upon similar processes in the enlarged thyroid. The far greater frequency of destructive and atrophic lesions of the adrenals in connection with symptoms of Addison's disease, however, makes the analogy of myxedema seem more reasonable than that of Graves' disease.

If this analogy prove true, should we not expect a therapeutic triumph similar to that over myxedema in those cases of Addison's disease where the adrenal inadequacy is not overshadowed by the strong toxic influence of extensive tuberculosis? Dubois,[18] taking the ground that the disease is a continuous autointoxication from the lack of an excretory action of the adrenals, says in confirmation of that view that the therapeutic use of capsular extracts by injection always produces toxic phenomena and hastens death. But of late we know that some definite observations have shown the opposite fact. Cases have been reported by Osler,[17] Shattuck,[19] Deeks,[20] Porpelow,[21] and others, showing marked improvement and in some

cases cure of the disease, with disappearance of bronzing, under the administration of adrenal extract. There is certainly ground for encouragement in trying this remedy wherever advanced tuberculosis is not present.

Dr. M. Foster[22] points out that the cortex of the adrenals is derived from the masses of mesoblastic cells surrounding the great blood-vessels, while the medulla is derived from and is a modification of the sympathetic ganglia. The former suggests important metabolic processes, some of which are connected with the history of pigments of the body at large. The latter suggests peculiar nervous connections. In some animals he adds that these two are wholly separate bodies. Probably the more important functions of the organ reside in the medulla, in which, for instance, Abel[23] finds that the blood-pressure raising constituent is contained. The total extirpation of the adrenals is fatal.

Two views have been held as to the function of the adrenal glands —one expressed by Huisneau[24] that they attract to themselves certain toxic products originating from intestinal decomposition (*e. g.*, pyrocatechin) and from muscle action (*e. g.*, phosphoric and lactic acids), rendering them harmless and preparing them for excretion by the kidneys. The other, that there is a synthetic production of a substance essential to the maintenance by the sympathetic system of the nutrition and normal tone. The latter view is at present most favored by physiologists. But it is perhaps easiest to explain the symptoms of Addison's disease by assuming that both these functions are fulfilled by the adrenals. The failure of the first explains the toxemia, the failure of the second the pigmentary and other nutritional changes.

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TWO CASES OF RENAL TUBERCULOSIS ILLUSTRATING THE RESULTS OF NEPHRECTOMY.

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CASE I.—On November 10, 1897, I was consulted by Mrs. X., aged forty-six years, married, occupation housewife, who gave the following family history: Her mother died of pulmonary tuberculosis, contracted during the patient's intrauterine life, four years after the patient's birth; her father died of an acute "fever" after a few days' illness; she had two brothers, one of whom died of some acute "fever," and the other of pneumonia; two sisters are living and in good health.

Personal History. Patient was well and strong as a child; puberty occurred at fifteen, menses were regular, but painful and profuse. She had the usual diseases of childhood and youth, without complications or accidents; was married at the age of twenty-one years; two years after she was delivered of a healthy male child, who died of "heart disease" at the age of seventeen years; no miscarriages or symptoms of uterine or ovarian disease. In the spring of 1880 the patient had a slight pulmonary (?) hemorrhage, and another in the fall of the same year, and this experience continued every spring and fall for ten succeeding years, after which it ceased entirely. The cervical glands became enlarged about this time, and remain in the same condition now. In the winter of 1890 she began to have a dull, deep pain in the right posterior costoiliac region, which was regarded as lumbago, and about the same time she had painful and profuse micturition, but her statement that she sometimes passed "two gallons of urine in twenty-four hours," must, I think, be taken *cum grano salis*. It was soon observed that the urine became cloudy and less abundant, although the cystic irritation and imperative demands to urinate increased from day to day. A diagnosis of cystitis was now made, and she entered upon a "course of treatment" consisting of a great variety of drugs, frequent and persistent cystic irrigation, and, finally, opening or "buttonholing" the bladder through the vagina, so as to give the bladder perfect rest and afford an opportunity for free irrigation. After a few weeks the vesicovaginal opening was closed, and the patient was dismissed, with the symptoms practically unchanged. Now ensued a period of between one and two years of constant suffering, progressive failure of health,

loss of flesh and strength, and, most of the time, the employment of what was called "expectant treatment." This brings the case down to the time that I was first consulted, namely, November 19, 1897. At that time the patient's condition was pitiable indeed. She was much emaciated, her weight having fallen from about 120 to 80 pounds. Her temperature ran from 100.5° in the morning to 103.5° in the afternoon; her chief occupation seemed to be to respond to the unintermitting calls of her bladder, which never contained more than 10 c.c. to 20 c.c. of urine, but never seemed empty; she had frequent rigors, followed by profuse sweating; her digestion was greatly impaired, gastric and intestinal flatulence and constipation being the ruling symptoms. The urine was scanty, strongly alkaline, offensive, and thick with pus and phosphatic deposit; the specific gravity was 1025; urea 2.3 per cent.; albumin 0.5 gram per liter; no sugar; pus and epithelial cells in great numbers; a few blood globules; a copious deposit of earthy phosphates and much granular debris. Streptococci and colon bacilli were abundant, but I could find no tubercle bacilli. Cardiac sounds were weak, but otherwise normal. The patient complained of a constant pain in the back to the right of the spinal column, varying from a very endurable dull ache to a sharp and agonizing misery, but always in the same place.

Physical examination disclosed the presence of a rounded mass in the right lumbar region, extending backward into the costoiliac space, easily grasped between the hands placed anteroposteriorly, quite movable, indistinctly nodulated, semi-fluctuating and very tender. This mass was reniform in outline, but apparently 50 per cent. larger than the normal kidney.

The patient was sent at once to Wesley Hospital, and on the following day, after thoroughly irrigating the bladder, I obtained a specimen of urine from each kidney separately, by means of M. L. Harris' "segregator." The findings in the urine from the right kidney were almost an absolute duplicate of those already recorded; the urine from the left kidney contained a trace of albumin, a few leukocytes, but no blood or tube casts, while the urea was a trifle over 2 per cent. No attempt was made to use the ureteral catheter, because the diagnosis seemed clear enough without it, and the patient's condition did not warrant any needless instrumentation.

Operation. The patient and her husband (himself a physician) were now told that the only hope lay in an operation, which might involve nephrectomy, and would at the very best involve danger, but they promptly decided to have the operation at once. Accordingly, on the afternoon of November 15, 1897, I made an exploratory incision from the lower rib just outside the anterior border of the erector spinæ, downward and a little forward, to the middle of the iliac crest, my intention being to expose the kidney, and then act as circumstances and conditions dictated. The kidney was easily reached and rapidly exposed; it was found enlarged and much disorganized; beset by several cavities the size of English walnuts or larger, containing thick, cheesy pus, very suggestive of tuberculosis. But, as the patient was beginning to show marked indications of exhaus-

tion, I did not deem it wise to expose her to the added risk of nephrectomy, and I therefore rapidly evacuated the pus cavities, irrigated with lysol solution and closed the wound, expecting a fatal result in a few hours. But the patient slowly rallied, and entered upon a tedious convalescence; the immediate distressing symptoms were much relieved, the bladder became more tolerant, digestion improved, she began to gain flesh slowly, the temperature fell to normal and in all respects her condition was much more encouraging. Meantime microscopic examinations of the contents of the renal pus cavities showed the presence of tubercle bacilli and established the diagnosis of tuberculosis of the right kidney. Tubercle bacilli now began to infest the purulent matter passed from the bladder, but repeated segregation failed to reveal the bacilli in the urine from the left kidney, while the urine from this kidney remained clear and transparent, although it still contained a trifle of albumin and a few leukocytes, but no casts. The operation wound did not close, but a urinary fistula resulted, which became a serious source of annoyance and danger. In view of all these unfavorable conditions relating to the right kidney it became obvious that the risk of nephrectomy must be taken or the patient must be allowed to wear out by inches; as the left kidney appeared to maintain its structural and functional integrity, it seemed to me that the operation was not only justified but demanded, especially as the patient and her husband fully understood its dangers and urged me to operate. Accordingly, on February 1, 1898, I removed the right kidney through the lumbar incision already described. The operation was rather tedious on account of adhesions, but I succeeded in separating the kidney from its attachments by blunt dissection, without accident. The patient was in a state of extreme exhaustion at the close of the operation, and for the next twelve hours the result hung in doubt. After that she began to gain, at first slowly, and then more rapidly, finally making a good recovery. She was under my care off and on until June 11, 1898, when she was discharged, with her health vastly improved and still improving.

I saw her last on July 28, 1903. At that time her temperature was normal; weight 113 pounds (against 80 pounds in November, 1897); she appeared ruddy and healthy, and said she "never felt better in her life." Urine was normal in quantity; slightly cloudy with mucus; acid; specific gravity 1020; urea 2.75 per cent.; no albumin or casts; there was some bladder or vaginal epithelium and a few leukocytes; there were no tubercle bacilli, but a few colon bacilli. The left kidney was easily felt, but was not tender or nodulated. It had evidently undergone physiologic hypertrophy and is doing the work of two kidneys. It therefore seems entirely correct to class this case as one of perfect recovery.

CASE II.—June 15, 1903, Miss Y., aged thirty-nine years, single, occupation nurse, consulted me and gave the following family history:

Family History. Father living at the age of seventy-three years and healthy, with the exception of "rheumatic pains" during spring and fall; mother died at the age of sixty-three years of "organic disease of the heart;" three brothers are

living and in good health; five sisters, all living and in fairly good health; no history of tuberculous disease on the part of any member of the family.

Personal History. The patient had always been well and strong until recent years. She had lived an active country life until she began nursing, a few years ago; had had no severe illnesses or bodily injuries; in fact, her history was that of a healthy and strong woman until rather more than three years ago, when she was much exhausted by constant nursing and had some "soreness" of the joints and "weakness" as a result. About three years ago, also, she began to have frequent and urgent calls to urinate and attacks of pain, which was referred to her right kidney. In April last—or three months before she consulted me—she had hematuria and sharp pain in the right costoiliac space, following sudden and forced stooping or bending the body forward as far as she could, and then righting herself by violent muscular effort.

At my first examination, June 15, 1903, she appeared sallow and weary; her temperature was 100.5°; pulse varying from 80 to 90; she weighed 150 pounds, having lost ten pounds during the preceding two months; her digestion was poor, bowels irregular, and she was much annoyed by intestinal flatulence. She complained of pain and tenderness, which was located in the right kidney, both pain and tenderness being aggravated by exercise or muscular effort of any kind. She was greatly distressed by frequent and urgent calls to urinate, both day and night, and stated that the urine was both scanty and offensive.

Physical examination at this time showed heart and lungs normal, stomach and bowels healthy; liver slightly enlarged; menstrual function undisturbed. In the right costoiliac space I found a tumor somewhat larger than a normal kidney (which it resembled in form) movable, tender, but without palpable nodulations or irregularities. Paroxysms of pain extended down the course of the ureter into the bladder, and were accompanied by urgent calls to urinate. The urine was pale, offensive, and turbid with pus; acid; specific gravity 1010; urea 1 per cent.; albumin 0.5 gram per liter; no sugar; pus cells in great abundance; numerous bladder and renal epithelium; a few blood globules, but no tube casts. The daily output was not stated. Urinary segregation demonstrated an apparently healthy left kidney, while the flow from the right kidney contained all the pathologic factors enumerated above. I must frankly admit that no bacteriologic examinations were made at this time, as the presence of pus germs might be safely assumed and the presence of tubercle bacilli was not suspected.

A "working diagnosis" of suppurative pyelonephritis with probable renal calculus was made, and the patient was informed that operative interference would be required. But as she preferred to try "medicine" for awhile, she remained under my care as an office patient for a couple of months, taking diuretics, antiseptics and tonics, alternately or combined, without any benefit, or any appreciable harm.

September 24, 1903, she entered St. Luke's Hospital, Chicago, and the following day I made a cystoscopic examination of the bladder, which showed a well-

marked cystitis, but nothing else; the urine could be plainly seen trickling from each ureteral orifice, that from the right kidney being turbid and slightly bloody, that from the left kidney being clear and normal in color. Urine obtained from each kidney by means of the segregator gave substantially the same results. Specimens of the urine examined in the hospital laboratory gave practically the results recorded before.

Obviously the case could only be reached by surgery, and so on September 26th I operated, expecting to find a suppurating kidney and most probably a calculus. To my great surprise I found a kidney considerably enlarged and presenting several fluctuating nodulations, each one larger than an English walnut and filled with rather thin pus in which floated bits of cheesy matter, very suggestive of tuberculosis. Upon exploring the kidney in my vain search for a calculus I found that the entire organ was beset with similar cavities filled with similar contents. I therefore proceeded to remove the kidney entire, fortunately without accident or complication. The patient recovered in an uneventful way and was discharged October 20th with normal temperature and otherwise in good condition.

Microscopic examination of smears from the pus cavities in the kidney showed numerous tubercle bacilli and giant cells were found in sections from the surrounding tissue.

Examination of the patient's urine, April 22, 1904, gave the following results: color, amber; reaction, acid; specific gravity, 1012; albumin, very slight trace; no sugar; few leukocytes and epithelium; very few small hyaline casts, which give no amyloid reaction; no tubercle bacilli; few colon bacilli. The patient wrote that "her temperature is normal" and that she had "gained thirty pounds since last October."

The history, symptoms, and results seem to indicate that this was a case of primary tuberculosis of the kidney cured by the prompt removal of the diseased organ. Of course, the ultimate result is a question for future consideration.

My experience in the examination and treatment of renal growths has led me to adopt certain conclusions which I am disposed to regard as axiomatic.

1. There is no royal road to the certain diagnosis of the nature or pathology of renal enlargements. It is impossible to differentiate with absolute certainty a simple renal hypertrophy from a tumor, especially when, as it occasionally happens, that the hypertrophy is more or less asymmetric or when a neoplasm differs but little in shape or density from the kidney which it has invaded. But when we come to the problem of deciding as to nature or pathology of a renal growth, the difficulty is very much increased, and in fact, the question is one which it is impossible to answer, except by negatives, prior to an operation. But it is a matter for congratulation that the

time has come when renal tumors are no longer mistaken for ovarian tumors, as was formerly so often the case.

2. It seems to be a comparatively rare thing to discover tubercle bacilli in the urine; it certainly is in my own experience, although I have diligently and carefully sought for them very many times, and most of my confrères here in Chicago tell me that they have had the same experience. Several new methods, or rather improvements in technic, have been proposed recently, but I have not yet been able to give them satisfactory trials. One difficulty is that of being able to discriminate with absolute certainty between smegma bacilli and tubercle bacilli, but thorough alcoholic decolorization of carbol fuchsin stains, after previous decolorization with nitric acid, would seem to solve that difficulty. Of course, the trained bacteriologist working in a hospital laboratory would have no difficulty, but the confusing resemblance between tubercle and smegma bacilli might lead a comparatively inexperienced practitioner far astray in his diagnosis. J. Bergen Ogden, in his admirable *Clinical Examination of the Urine*, gives very clear and concise directions for the examination of urine for tubercle bacilli, the gist of which is that the suspected pus should be twice washed in distilled water, then stained in the usual manner with carbol fuchsin, then decolorized with nitric acid, and afterward decolorized for at least ten minutes with 70 per cent. alcohol. The specimen is now ready for staining with methylene blue and mounting for examination. Improved methods will without doubt enable us to detect, with certainty and facility, tubercle bacilli in the urine, but up to this time it must be said that their detection in urinary deposits is uncertain and unreliable as a means of positive diagnosis.

3. Primary tuberculosis of the kidney, while not common, is not so rare that it can be left out of our calculations in any case of renal tumor. The fact that tuberculous disease has not appeared in any other part of the body is of little account as an argument against the possibility of tuberculosis of the kidney, in spite of the common belief to the contrary. It must be remembered, also, that other deposits of tubercle, too small or too obscure for detection, may be present, so that it is hardly safe to assume that any case of renal tuberculosis is positively primary without the most searching examination of all accessible portions of the body. Furthermore, this rule holds good in the case of children as well as adults, hence no case can be considered exempt therefrom.

4. The great majority of kidney operations must be regarded as exploratory and diagnostic. No operator, however experienced, can be sure what he is going to find when he exposes a diseased kidney. Those who have had the greatest experience in renal surgery can look back upon their surprises and disappointments, as evidenced by cases in which the exposed kidney told a very different story from what the preoperative diagnosis indicated. Of course, this is not peculiar to renal operations, but of late the idea has arisen that, owing to improved means of diagnosis, a marked degree of certainty has been reached with respect to the diagnosis of surgical diseases of the kidney. But in spite of all our refined methods, backed up with the highest degree of skill and the largest experience, the diagnosis of the surgical lesions of the kidney, and especially renal neoplasms, is still to no small extent a matter of conjecture, as every candid physician or surgeon must admit.

For many years past I have preferred to operate on my own cases of renal disease. A physician cannot divest himself of his responsibility for or his interest in a case by simply turning it over to a surgeon; neither can he expect the surgeon to act simply as an assistant for the purpose of carrying out the physician's wishes. Moreover, the postoperative treatment, both medical and surgical in a case of surgical kidney, is frequently of quite as much importance as the operation itself. For these and other reasons I have preferred to retain complete control of my cases of surgical kidney, and also to do my own operating; and I feel quite justified in recommending a similar course to other physicians who are giving special attention to renal diseases. The operation presents no difficulties which ought to appear formidable to any physician of experience; the incisions are simple, the landmarks plain and the organ is easily reached and delivered. The physician who has studied the patient and the symptoms relating to the diseased organ for weeks or perhaps months prior to the operation ought to be the best judge of the measures most appropriate for the case in hand after the kidney is exposed; but if he is only an "innocent bystander" he can have very little to say about it. Again, the after-treatment is important from a purely medical standpoint, and on this account the physician ought to keep his cases under his own control; at least I have found it most advantageous to my own patients. To avoid any possible misapprehension of my meaning, I add that I have invariably received the most liberal, courteous and friendly treat-

ment from the surgeons with whom I have been associated in my practice.

In concluding this paper I cannot forbear congratulating the profession and the laity on the tremendous advance in our knowledge of the pathology and treatment of renal diseases—especially those of a surgical nature—since my advent to the profession in 1862, when the kidney was "beyond the reach of the surgeon" and our medical professors dismissed "Bright's disease" with only one positive assurance, namely, that the patient was sure to die.

CONCERNING HEMAGGLUTININS OF BACTERIAL ORIGIN AND THEIR RELATION TO HYALINE THROMBI AND LIVER NECROSES.*

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Elsewhere one of us[1] has decribed the hemagglutinative power of various cytolytic immune sera and the relation of the red blood corpuscle thrombi (hyaline thrombi) resulting from the injection of such sera to focal hyaline necroses of the liver. The distinct character of the liver lesions thus produced, and the fact that they could be explained only by the presence of agglutinated red blood corpuscle thrombi, suggested the possibility that similar lesions occurring in various infectious diseases might be due to the development of hemagglutinins of bacterial origin. In order to test this supposition we have attempted to demonstrate the presence of hemagglutinins in filtrates of bacteria treated in various ways, and by the injection of the same into animals to produce agglutinated red blood corpuscle thrombi and associated liver necroses.

It is not our intention to go into the general literature of these subjects, but merely to touch upon those points which relate to infectious conditions. The more important views concerning liver necroses may be found in the papers of Flexner,[2] Mallory,[3] Boxmeyer[4] and Opie.[5] That the so-called hyaline thrombi may be composed of altered and fused red blood corpuscles we consider to be definitely established. The recent studies of Flexner,[6] Boxmeyer and Pearce offer conclusive evidence of such origin and

* This study has been conducted under a grant from the Rockefeller Institute for Medical Research.

support the earlier observations of Klebs[7] and Ziegler.[8] The occurrence of hyaline thrombi in connection with various infectious and toxic conditions has been emphasized by Welch,[9] who, in his summary of the literature, mentions particularly infections with S. pyogenes aureus and B. choleræ suis, and offers a suggestion concerning their origin from red blood corpuscles. In a later discussion[10] of the subject he brings forth the hitherto unpublished observation of Fisher concerning the plugging of small vessels by agglutinated red cells as the result of injecting typhoid bacilli, and calls attention to the evidence in favor of the interpretation of many of the hyaline thrombi as derived from fused red blood corpuscles. Other important observations are those of Flexner, who found similar thrombi in the intestine of typhoid fever, in bronchopneumonia and in experimental diphtheria; and also of Boxmeyer, who could distinguish, in the livers of rabbits dying of experimental hog cholera, between necroses due to endothelial cell thrombi and those due to agglutinated red blood corpuscle thrombi. The hyaline thrombi occurring in various intoxications, due to either organic or inorganic poisons, and in toxic conditions of doubtful origin, as eclampsia, are undoubtedly of similar nature; but as they do not come within the scope of this study, will not be further considered.

Of considerable historical interest in connection with this question of the occurrence of red blood corpuscle thrombi in the course of infectious diseases are the observations of Hueter,[11] made in 1873. As the results of his studies, to which attention has recently been called by Welch,[10] Hueter came to the conclusion that clumping of red blood corpuscles, causing permanent or transient occlusion of capillaries and small vessels ("globulöse Stase und Embolie") occurred not uncommonly in septic and other fevers. His theory that this phenomenon constituted the underlying basis of fever has never gained acceptance, but the observations are of interest in connection with our recently acquired knowledge of bacterial hemagglutinins. v. Recklinghausen[12] considers this globular stasis of Hueter to be analogous to a condition found in the capillaries after transfusion of alien blood, and which he describes as an "agglutination" of red blood cells.

In planning this investigation it was evident that as necroses of the liver are most frequently associated with infections by the bacillus of typhoid fever and the bacillus of hog cholera, the bulk of the work should be done with these organisms. In order, however, that no opportunity might be lost, the literature dealing with bacterial hemolysins was examined in the hope of finding reference to organisms which produced also hemagglutinins ; of twenty-nine such investigations[13] but six[14] refer to the production of hemagglutinins by bacteria. Kraus and Ludwig found that bouillon cultures of S. pyogenes aureus and Vibrio Paris had the power of agglutinating red blood corpuscles *in vitro* in from ten to twenty-four hours at room temperature. The mass which settled at the bottom of the tube was seen upon agitation to be composed of small clumps of red blood corpuscles which could not easily be disintegrated. The agglutinin they considered to be independent of the hemolysin; but, on the other hand, they state that organisms which do not hemolyse also do not agglutinate. Small amounts of the cultures caused agglutination without hemolysis. Volk and Lipschütz, working with staphylolysin and vibriolysin, describe agglutination in connection with incomplete hemolysis of rabbits' blood, but did not observe it with other bloods. Volk, as a result of his observations, comes to the conclusion that agglutination is due not to a specific body, but to non-isotonicity of the fluid. Calamida states that no agglutination precedes the hemolysis caused by bouillon cultures of the chicken-cholera bacillus. Flexner mentions agglutinins of low activity in filtrates of B. pyocyaneus, B. typhosus and S. pyogenes aureus. Kayser, in his study of colilysin, observed a clumping of red cells in connection with incomplete hemolysis, but not when complete solution occurred. Of greatest interest, however, and very suggestive, is the observation of Eisenberg,[15] who found the blood of an individual with a generalized pyocyaneus infection to be both autoagglutinative and isoagglutinative.

As the result of this survey, it seemed advisable to utilize B. pyocyaneus and S. pyogenes aureus in addition to B. typhosus and B. choleræ suis ; and these, with B. dysenteriæ and S. pyogenes, constituted the group of organisms finally selected for study.

METHODS. In previous attempts (Reed,[16] Flexner, Mallory and Boxmeyer) to produce liver necroses by the injection of micro-organisms, either the living culture, grown in the ordinary way, or its filtrate has been used. With the use of the former it has been difficult to distinguish between the direct action of the organism and the effect produced by its toxin; with the latter the action of intracellular toxins has been excluded. In our experiments the direct action of the micro-organisms has been eliminated by the use of filtered fluids, and an attempt has been made to obtain the intracellular constituents of the bacterial cells by the utilization of methods destined to cause its disintegration. Various writers have described methods by which the bacterial cell is destroyed and its receptors liberated. Of these methods we have tried, with certain modifications, the processes of autolysis described by Conradi,[17] Neisser and Shiga[18] and Brieger and Mayer.[19] The various organisms have been grown for twenty-four to seventy-two hours on agar, in large flat flasks having a surface of 20 x 8 cm. The growth on several flasks, usually three or four, has then been scraped off, subjected to 55° C. for forty-five minutes, and placed in tubes containing 0.85 per cent. salt solution at a temperature of 37.5° C. for two to three days. In some instances the fluid has stood for longer periods, varying from one to seven weeks. The fluid has then been filtered (Chamberland B. and F.) and injected intravenously into animals after testing its agglutinative power *in vitro*. At various stages of the process suitable controls were made to demonstrate absence of contamination and the efficiency of the filters.

In addition to this method of growing the organism, an attempt was also made to stimulate the production of hemagglutinin by previously growing the organisms in media containing red blood cells. This method was suggested by the theory of "bacteriogenic cytotoxins," advanced by Welch in his Huxley Lecture: "Certain substances of the host of cellular origin, assimilated by the parasites through the possession of haptophore groups with the proper affinities, become anchored to receptors of the parasitic cell, which, if not too much damaged, is thereby stimulated to the overproduction of like receptors; these excessive receptors of the parasite, if

cast off into the fluids or the cells of the host, then constitute intermediary bodies," etc. The writer further states: "By a similar mechanism it is possible that parasites may be stimulated to the production also of antibodies other than cytotoxins, such as various agglutinins, precipitins, antienzymes—all adjusted against the host."

Assuming that if this hypothesis might apply to organisms growing in living cells or fluids, it might hold also for those grown on cells outside the body. Typhoid and hog cholera bacilli have been grown in various blood preparations. These include both defibrinated and washed blood added in various proportions to salt solution and fresh sterile rabbits' organs. The period of growth in the various blood mixtures varied from twenty-four to seventy-two hours; in some instances inoculations into fresh blood solutions or upon fresh organs being made on each of three successive days. The sterile organs were prepared according to the technic described by Flexner.[20] By these various methods it was hoped that the organism would be stimulated to produce agglutinins and that this power would be retained during the subsequent growth on agar, giving in the finished autolyzed product a fluid of appreciably augmented agglutinating power. Observations supporting this theory have been made by Marmorek and by Simon, who found that streptococci grown in media composed of leukocytes alone or with bouillon added secrete a toxin of considerable power. Simon[21] believes that the streptococcus in order to secrete toxin must meet a certain resistance to its development and that this resistance is furnished by something in the leukocytes. This explanation, put in the terms of Ehrlich, corresponds to Welch's hypothesis. Our attempts to produce free agglutinin receptors by growing the organisms in blood we consider analogous to Simon's method of producing toxin by growth in leukocytes.*

Another method employed was the growth of an organism in

* Another point in favor of this theory of bacteriogenic antibodies is the observation of Theobald Smith (verbal communication) that recently isolated cultures of the hog-cholera bacillus have a greater power to produce liver necroses than have old cultures. Accepting Boxmeyer's work on the relation of agglutinative red blood corpuscle thrombi to such lesions the explanation naturally suggested is that residence in the animal has stimulated the power of the bacillus to produce agglutinin.

heated rabbit serum. This was suggested by the observation of Besredka,[23] that the streptococcus produces an hemolysin when thus grown.

Results. The tests for agglutination were made by adding nine parts of the various filtrates to one part of blood. Observations were made at room temperature and at 37.5° C. at varying periods up to twenty-four hours. The clumping of red blood corpuscles by bacterial hemagglutinins is of slight degree as compared with that produced by various cytolytic immune sera. The powerful agglutination of the latter is never seen, and for this reason more careful comparison with controls is necessary in order to detect slight differences in reaction. This feeble activity renders it difficult to make definite statements concerning some of the organisms studied. While all (B. typhosus, B. choleræ suis, B. pyocyaneus, B. dysenteriæ, S. pyogenes aureus and S. pyogenes) in the majority of tests *in vitro* showed a slight agglutination as compared with controls, the effect of filtrates of B. dysenteriæ, B. choleræ suis and B. pyocyaneus was so slight as to be considered doubtful. With other organisms the agglutination was more evident, being most distinct with filtrates of S. pyogenes. Upon microscopic examination (hanging drop) the clumping caused by the streptococcus was always in the form of massive, more or less branching rouleaux, while with all other cultures an irregular agglutination of a small number of corpuscles was seen. The agglutination due to the streptococcus could be seen after fifteen to twenty minutes, as the corpuscles settled, while with the other organisms it could be seen only upon agitation after a considerable period of time. More definite results were obtained with rabbits' blood than with dogs' blood.

Of unusual interest and very suggestive are the agglutination tests with filtrates of typhoid bacilli previously grown in blood suspensions and on fresh sterile organs; though carried out in but a small number of tests, they appear to be confirmatory of Welch's hypothesis mentioned above. These filtrates, especially those of bacilli grown on sterile organs, exhibit an appreciably greater power of agglutination than the filtrates of organisms grown on agar only.

While no effort was made to study especially bacterial hemolysins, it is of interest that the autolytic products of bacteria as here prepared have never caused hemolysis. This result is in harmony with the observations of Jordan,[23] Williamson[24] and others who hold that the hemolysis produced by many bacterial filtrates (B. typhosus, B. pyocyaneus) is to be explained by the presence of an alkali elaborated in the growth of the organism. The filtrates used in our tests have all been faintly acid to phenolphthalein.

The animals selected for the injection experiments were dogs and rabbits; the former receiving 5 c.c. to 20 c.c. (dose 1 : 1514 to 1 : 235) of the filtrates in either the saphenous or mesenteric vein; the latter 1 c.c. to 20 c.c. (dose 1: 1790 to 1: 64) in either the mesenteric or marginal ear vein. In all, twenty-nine injections have been made; in no instance did death occur as the immediate result of the injection. Necroses of the liver occurred in ten of the animals. Two of these we have thought best to exclude because of associated coccidiosis, although the necroses appeared to be entirely independent of the parasitic invasion; another has been excluded also because of the chronic character of the lesion. The remaining seven cases exhibited typical necroses; two occurring in dogs and five in rabbits. These lesions followed the injection of filtrates of the typhoid bacillus in three cases, of the hog-cholera bacillus in three cases and of the dysentery bacillus in one case. Filtrates of the B. pyocyaneus, S. pyogenes aureus and S. pyogenes did not cause necroses. These necroses are not always visible to the naked eye, but when seen macroscopically they appear as miliary points, or occasionally as round or oval areas or linear streaks of grayish color, and distinctly separated from the normal liver tissue. They are very few in number compared to those produced by the agglutinins of cytolytic immune sera, and are usually limited to the superficial portions of the liver lobes. Portions of the liver in contact with other lobes or adjacent organs are more frequently involved than the free surfaces. Histologically, the liver cells exhibit a hyaline necrosis, the nuclei being entirely destroyed, or evident merely as faint rings; fragmented or pyknotic nuclei were seldom seen. In many of these areas the vessels are filled with red blood corpuscles more or less altered and

fused and suggestive of hyaline thrombi. This condition, however, is not constant, and is not so evident as in the necrotic lesions produced by cytolytic immune sera. On the other hand, larger vessels, especially the smaller branches of the portal vein, contain typical agglutinative red corpuscle thrombi more or less completely occluding the vessel. Similar thrombi of small vessels have been seen in other organs, as the kidney, spleen and lymph nodes, but without definitely associated lesions. Other thrombi, as those composed of endothelial cells, fibrin, etc., have not been seen in the liver.

Fatty changes in the liver and kidney, intense congestion of the spleen and lymph nodes and a proliferation of the endothelial cells of the lymph sinuses have been found not infrequently after the injection of typhoid and hog cholera filtrates. A relation between these lesions and the injected fluids cannot, however, be readily demonstrated; the proliferation of endothelial cells especially is not infrequent in apparently normal animals. That some injury to the kidney is brought about is indicated by the appearance of albumin in the urine after the injection of filtrates of B. typhosus and B. dysenteriæ.

The results of the injection of filtrates of typhoid and hog-cholera bacilli grown upon blood media, while very suggestive, are not conclusive, owing to the small number of observations. But six filtrates so grown were injected. Filtrates of the typhoid bacillus grown in blood suspensions, while possessing an increased agglutinating power *in vitro*, did not cause necroses upon injection; on the other hand, two different filtrates of the same culture grown for several days on sterile rabbits' organs caused the most extensive lesions observed in the course of this investigation. The bacillus of hog cholera grown in blood suspensions caused, in one instance, lesions in the liver. The attempt to produce necroses with such filtrates has therefore been successful in three of six experiments; while with filtrates of the same organism grown on plain agar necroses resulted in three of twelve attempts. These results are suggestive in connection with the increased agglutinating power observed *in vitro*, but the small number of experiments does not warrant definite conclusions.

Filtrates of B. typhosus grown in heated rabbit serum produced no lesions upon injection into rabbits.

CONCLUSIONS. The filtered autolyzed products of a number of bacteria possess hemagglutinins of low activity, the formation of which may be stimulated by previously growing the micro-organisms on media containing fresh red blood cells. The injection of these filtrates into dogs and rabbits is followed in some instances by the occurrence of liver necroses with associated fused red blood corpuscle thrombi; like thrombi may occur in other organs. These thrombi are similar in structure to those generally described as hyaline thrombi. The demonstration of agglutination *in vitro* and the association of the fused red cells with the liver lesions suggest a relation of the agglutinin to the lesions. This relation, however, cannot be considered as proven, for it is impossible to exclude the effect of toxins acting directly upon the liver cells; on the other hand, the similarity of the lesion to the very definite necroses caused by the powerful agglutinin of cytolytic immune sera strongly supports the possibility of such a relation.

The results observed by us are in accord with the slight potency of the agglutinin obtained. It is probable that methods which cause a more complete disintegration of the bacterial cells, as those employed by Vaughan,[25] and by MacFadyan and Rowland,[26] would yield an agglutinin as powerful, comparatively, as the toxins so derived, and capable of producing lesions more analogous to those caused by the agglutinins of cytolytic immune sera.

We present this communication, therefore, not as an attempt to prove that all hyaline thrombi are composed of fused red blood corpuscles, or that all liver necroses are caused by such thrombi, but rather to indicate the evidence in favor of the view that these lesions, in some instances, may be due to bacterial hemagglutinins.

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PNEUMOPERICARDIUM.

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The presence of air in the pericardium is a surprisingly infrequent occurrence. I have been able to find records of but thirty-eight satisfactorily reported cases, including the one which I shall presently relate. The physical signs of this condition are more striking and characteristic than those of almost any other abnormal physical state of the body, and are so suggestive as to point directly to the correct conclusion, so that an error in diagnosis is not likely to occur. It seems, therefore, fair to assume that the paucity of printed records is a measure of the actual infrequency of the lesion.

For instance, Schrötter says: "The infrequency of the presence of air or gas in the pericardial space may be gathered from the fact that I have never had an opportunity of observing such a case in the course of my thirty-five years' diligent study of the enormous clinical material offered by the City Hospital (Vienna), while our predecessor and teacher, Skoda, had the same experience."

The condition seems to have excited far more interest in the early days of physical diagnosis than it does at present, and we find accurate descriptions of it in a number of text-books of that time; for instance, Stokes in 1855 related a case which came under his notice, and described clearly and vividly the extraordinary physical signs that are commonly present and which are characteristic of it.

Many of the earlier authors, also, noted and mentioned the very unusual anatomic appearances of the pericardium, which are hardly less extraordinary than are the physical signs (Meigs, Begbee, Morel-Lavallee). The case I have to relate is as follows:

K. N., aged twenty-five years, born in Ireland. Her father died of rheumatism. There is no history of rheumatism in her childhood, or, indeed, of any other serious illness. There was no chorea. She had always been well until six

months ago, when she suffered from a mild attack of acute articular rheumatism. At this time there was noted a soft systolic murmur at the apex of the heart, in the pulmonary area. There has been slight shortness of breath on exertion for the past few years. The appetite is good and the bowels regular.

Present Illness. While eating dinner she swallowed a small sliver of bone attached to a piece of meat from a mutton-chop. She was perfectly conscious of this at the time, and she herself dates all of her symptoms from this occurrence. At the time she felt pain under the sternum and was sure that the bone had lodged in the esophagus. There was then pain in both sides of the thorax, made worse by deep inspiration. Then nausea and vomiting came on, especially after the eating of solid food. There was slight diarrhea, the bowels moving from three to four times a day. There was also severe pain in the epigastrium, shortness of breath, cough and slight expectoration. Her chief complaint was abdominal pain and nausea. The above symptoms had grown steadily worse since the onset of the attack and she had been confined to her bed from the outset.

December 24, 1903. When first seen the temperature was 103.6°; pulse, 120; respirations, 32. The patient is fairly nourished, color sallow, somewhat cachectic, cheeks moderate hectic flush, expression anxious, surface of body hot and dry. Sensorium is clear, but on account of pain, dyspnea and discomfort she has some trouble in giving a satisfactory account of herself. Pulse soft, full, dicrotic, compressible and irregular; respirations rapid and somewhat labored.

Physical Examination. The chest is symmetric. The entire precordium is shaken by the beat of the heart; there is a visible pulsation in the great vessels of the neck, and the pulse in the suprasternal notch is well marked both to sight and touch.

The superficial lymph nodes are not enlarged.

Heart. The apex impulse is diffuse, forcible, with its maximum intensity in the fourth space, four and one-half inches to the left of the middle line.

There is tolerably marked tenderness to firm pressure over the lower one and one-half inches of the sternum and there is moderate edema of the skin over this area.

The percussion note over the right side of the chest in front is normal; the cardiohepatic angle also is normal.

Over the precordium to the left of the sternum there is pulmonary resonance, although the pitch is slightly higher than on the right side and the quality is somewhat tympanitic. There is no area of absolute cardiac dulness. The left border of the heart cannot be located by percussion.

When the patient takes a full breath and holds it there is heard by the listening ear, held twelve inches from the chest wall, a peculiar clicking sound synchronous with the cardiac systole; this click has a musical quality with the quality of a succussion sound or splash. It disappears with extreme expiration. Upon applying the ear or stethoscope to the precordium the heart sounds them-

selves are dull and muffled, but there are heard certain remarkable and unusual phenomena. The first sound is accompanied by a loud metallic tinkle of splashing, gurgling quality, suggesting the sound made by an old-fashioned overshot waterwheel, the *bruit de la roue hydraulique*. It is as if a very marked succussion were brought out by each systolic contraction of the heart, together with many metallic tinkles. This sound is heard loudest in the third, fourth and fifth left spaces and in the third and fourth right spaces. It is audible over the entire precordium. It is heard loudest during inspiration, rather less during expiration. Its intensity varies from time to time without apparent reason.

The above signs are obtained while the patient lies upon the back. When lying on the right side there is heard in the precordium, between the middle line and the left nipple, a typical to-and-fro pericardial friction sound, superficial, sharp and clear. In this position the splashing succussion sound and the metallic tinkle are not heard. When the patient lies upon the face, or rests upon the elbows and knees, the signs are the same as when lying upon the right side.

Lungs. There are numerous subcrepitant rales and coarse friction sounds heard in the left axillary region from the apex to the lower border of the lung. There are also a few subcrepitant rales in the lower right axilla.

The abdomen is moderately distended and tympanitic. There is no muscular rigidity.

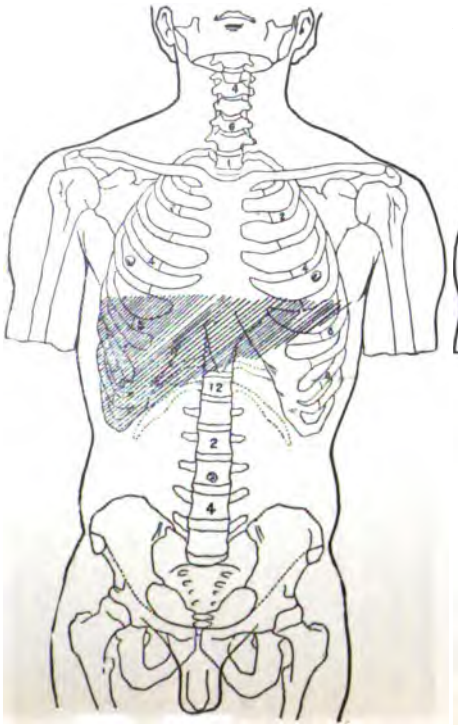
26*th*. The general condition is worse and the pulse is more feeble. There is no cyanosis; no marked dyspnea. The peculiar physical signs over the heart are the same.

A careful study of the heart dulness in different positions results as follows: When the patient is lying upon the back there is pulmonary resonance with slightly tympanitic quality over the entire precordium, as far down as the fifth costosternal junction, the line of dulness running about horizontally at this point. In this position the splashing succussion sounds and metallic tinkles are very marked. When the patient sits up the percussion note from the third left space to the fifth rib becomes distinctly more dull and the succussion sounds are heard clearly only at and above this line of dulness; much less below this point. When lying on the right side, there is an area of dulness extending laterally from the right border of the sternum to a point half an inch to the left of the left border of the sternum and longitudinally from the second interspace downward until it merges into the liver dulness below. Here also the metallic tinkle and succussion are heard at and above this line of dulness.

The accompanying three diagrams show the shifting dulness in different positions of the body. When the patient rests upon the elbows and knees, so that the chest is horizontal and the sternum looks downward, a to-and-fro friction murmur can be heard all over the precordium and the succussion and metallic tinkle entirely disappear.

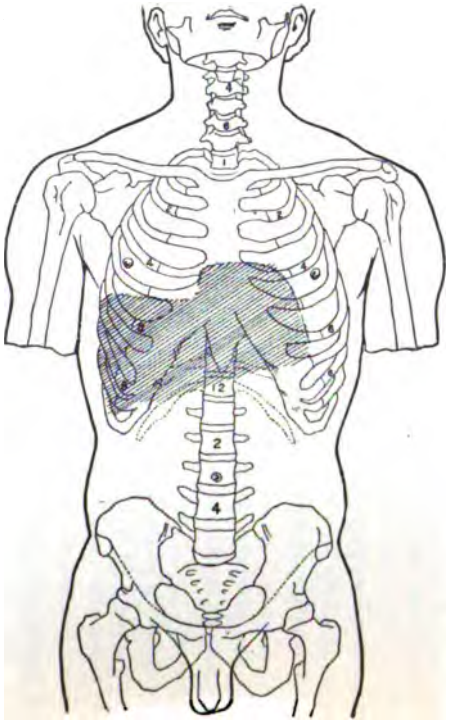
The leukocytes are 23,000 per cm., the temperature pursues an irregular course ranging from 102.5 to 105.8, as indicated upon the accompanying chart. The pulse is growing more rapid and feeble.

Fig. 1.



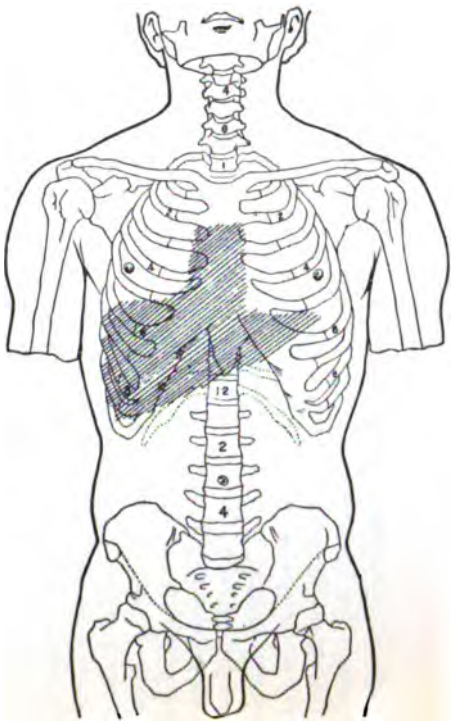
Percussion dulness, lying on back.

Fig. 2.



Percussion dulness, sitting up.

Fig. 3.



Percussion dulness, lying on right side.

In explanation of the above remarkable phenomena no other condition could be assumed than the presence of fluid and gas in the pericardium. An aspirating needle was then inserted in the sixth left space, two and one-half inches from the middle line, and withdrew half a drachm of thin, yellow pus. It was then decided to drain the pericardium, and immediately after the exploratory puncture the operation was performed by Dr. Joseph A. Blake.

Operation. Anesthesia. Quadrilateral incision was made over the precordium, exposing the fifth and sixth ribs, which were cut through about two inches from the sternum. The flap was then drawn forcibly back, fracturing the sternocostal attachments, thus exposing the pericardium. This was opened and there was a gush of extremely offensive gas. The parietal and visceral pericardia were found to be thickened, corrugated and coated with fibrin.

FIG. 4.

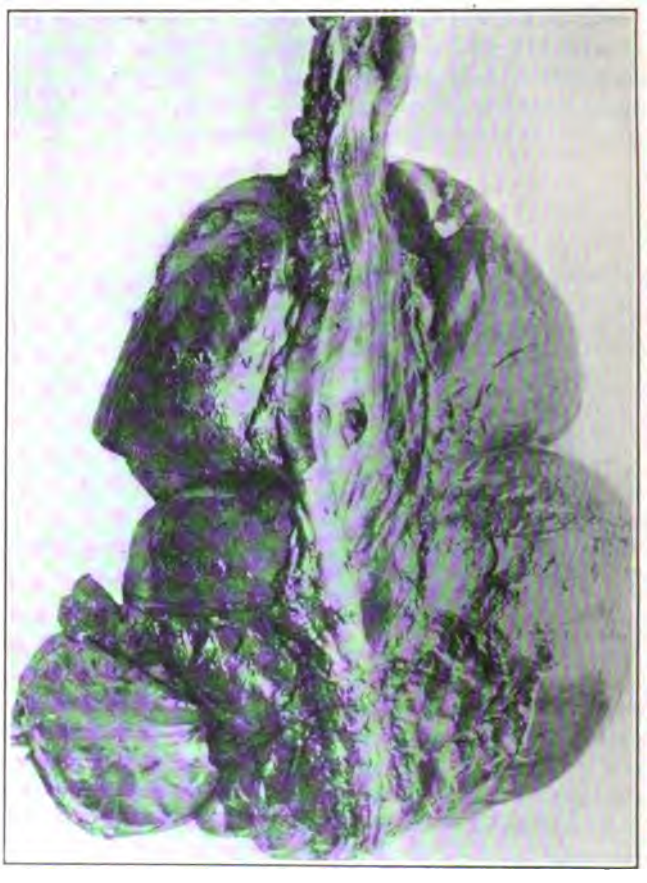
Heart and pericardium from front: white marker placed in perforation.

The pericardium contained a small amount, not more than two ounces, of thin, yellowish pus, which was found only upon lifting up the heart. The beats of the heart were forcible. No foreign body was found in the pericardium. The sac was irrigated with hot, normal salt solution, the flap was returned to its position, about half an inch having been resected from the sixth costal cartilage, two flat drainage tubes were introduced into the cavity and a dressing applied.

The patient made a good recovery from the anesthetic and for the next five hours was conscious, fairly comfortable and appeared to be no worse than before the operation. In a few hours, however, the pulse became more rapid, the temperature rose to 107°, and the patient died twenty-two hours after the operation, three and a half days after coming under observation, nine and a half days after swallowing the bone.

Autopsy, two hours after death. The left pleural cavity contains about 500 c.c. of cloudy, thin, yellow pus, which is foul swelling. The pericardium shows marked thickening of both layers, the epicardium being covered with a thin layer of foul-smelling, greenish, sticky pus. There is no free pus in

FIG. 5.



Heart from back; esophagus opened, showing perforation.

the cavity. Posteriorly, just below the root of the great vessels, is an oval opening, its long diameter being 1 cm., which opens obliquely into the middle of the esophagus. The parietal and visceral pericardia both present a very peculiar appearance. They are leathery in appearance, corrugated and deeply

fissured and are of a dirty, greenish-brown color. The appearance is peculiar and resembles most closely a piece of olive-green, crushed Levant morocco. The heart is normal in size, and there is no disease of its walls or valves. The lungs are congested and edematous. The spleen is about twice its normal size and congested. The liver shows slight venous congestion. On opening the esophagus, it is found to present two oval openings about 2 cm. long, directly opposite one another, perforating one into the pericardium, the other closely adherent to the left pleura.

Anatomic Diagnosis. Purulent pericarditis with perforations of the esophagus and pleura; congestion and edema of the lungs; congestion of the liver; left pyothorax. The most striking features of the above case are the peculiar succussion sound with metallic tinkle synchronous with the cardiac rhythm, and tinkling resembling the *bruit de la roue hydraulique* of the older French authors, and which could be heard at a distance from the chest. The change of the percussion area of the heart with change of position, tympany lying always uppermost, dulness below and the succussion and tinkle always at and above the line of dulness. Finally, the remarkable appearance presented by the pericardium after death, an appearance which coincides closely with the description of the lesion as given by several different authors who wrote almost half a century ago, and which I have never met with under any other circumstances. The symptoms of the case were so striking and peculiar that no other diagnosis than pyopneumothorax was possible from the outset, and this impression was confirmed by the puncture of the pericardium subsequently by operation and finally by autopsy.

The figures represent the anterior and posterior view of the heart and pericardium with aorta and esophagus attached.

I have found satisfactory records of 37 undoubted cases of this condition in addition to the one which I have just detailed. The etiology is varied.

In all but 5 cases there was an accidental communication between the pericardium and some other viscus, this being the origin of the pneumopericardium. In these 5 cases, however (Laub, Friedreich, Hawkins, Fetzer, Nichols), no perforation was found to account for the presence of the gas. In 1 case (Laub) the condition followed a sore throat and facial erysipelas; the physical signs were characteristic and the case went on to recovery, so that the origin of the gas was never discovered. In the remaining 4 the diagnosis was confirmed by autopsy, and no perforation could be demonstrated, thus indicating the possibility of the development of pneumopericardium from an inflammatory process. The possibility of pneumothorax originating from an infection by a gas-

producing bacillus, and without perforation, has been proved in a number of cases (Emerson); these cases are few in number compared with the total number of cases of pneumothorax. It is a very striking fact that in pneumopericardium a very much larger proportion of cases appear to have originated in this way, namely, 4 out of 35 cases.

In the case reported by Nichols the pericardial lesion followed emphysema which had complicated appendicitis. It was supposed that the bacillus aerogenes capsulatus was the etiologic factor, but no cultures were made.

Of the remaining cases (7) entrance of air into the pericardium was through the esophagus; in 3 of them (Chambers, Tuettel, Begbee) an ulcerating carcinoma of the esophagus opened into the pericardium. In one it is stated that an ulcer of the esophagus was the origin. While in 3 (Walshe, Buist, James) there was traumatic perforation of the esophagus. In the case of Walshe a juggler produced the lesion in the course of sword swallowing. In the case of Buist the patient swallowed a false-tooth plate of gold, which remained impacted in the esophagus for fourteen days, then ulcerated into the pericardium, producing a pyopneumopericardium which was discovered only at autopsy.

In 8 cases (Aran, Flint, Bodenheimer, Gruttner, Müller, Audry, Feine, Dolbeau) the cause was a penetrating wound of the pericardium from without. In the case of Aran it followed paracentesis of the pericardium.

In 4 cases (Müller, McDowel, Pelcs, Combemale) there was softening of a neighboring tubercular focus either in the lung or in a lymph node, with the formation of a fistulous communication between the pericardium and either the lung or the esophagus.

In 7 cases (Müller, Iæonpacher, Steiger, Morel-Lavallee, Bricheteau) the condition followed an injury which produced fracture of ribs or sternum, with wounding of the lung, and presumably tearing of the pericardium, without external wound.

In 2 cases (Graves, Nichols) an acute inflammation in the abdomen was the starting point. In the case of Graves an abscess of the left lobe of the liver perforated into the pericardium. In the case of Nichols there was first appendicitis, then pleurisy with effusion, pneumonia and empyema of the right side, followed by pyopneumopericardium. At the autopsy gas and pus were found in the pericardium, but no perforation was discovered, and the

condition was supposed to be due to the presence of a gas-forming bacillus.

In 2 cases (Saexinger, Guttman) a gastric ulcer perforated into the pericardium.

In 1 case reported by Müller there was first empyema on the left side, then purulent pericarditis, which later perforated into the left lung, with the free passage of pus through the bronchi and development of pyopneumopericardium. This case recovered.

In 1 case (Eisenlohr) there was first pneumothorax, then a perforation into the pericardium.

In the case of Sievers pneumonia was followed by gangrene of the apex of the left lung, which subsequently perforated into the left pleura, and then into the pericardium.

In the case of Meigs some disease of the lung of unknown nature produced perforation into the esophagus, and later from this a perforation into the pericardium.

In the case reported by Stokes there was first acute pericarditis, which went on to hydropneumopericardium and then to complete cure, the origin of the gas not being discovered.

The physical signs of the condition were strikingly uniform in most of the cases.

In 1 case there was cracked-pot resonance; in 21 the normal pericardial dulness was replaced by tympany. In only 3 (Laub, Feine, James) was there special mention made of the shifting relation between the pericardial tympany and the adjacent dulness with change in position, and in these the tympanitic area always occupied the uppermost portion of the pericardium, dulness being present below.

The most characteristic sign is a splashing, gurgling sound synchronous with the heart beats, and variously described by different observers. By the French it was called "bruit de moulin" or "bruit de la roue hydraulique," from its resemblance to the noise made by a waterwheel. It has been likened also to the sound made by an old-fashioned wooden churn (Meigs). Its character is unmistakable, and it can hardly be confounded with any other sound heard in physical examination.

A possible source of confusion might arise from hydropneumothorax, succussion being produced by the action of the heart, and the sounds being transmitted to the precordium. In pneumopericardium, however, the sounds are far louder, are heard most dis-

tinctly over the heart itself, while the study of the relation of the signs over the precordium to those over the rest of the chest on either side, together with the study of the changing area of precordial dulness with change of position, ought to prevent error.

Stokes, after describing the physical signs, says: "In the whole of my experience I have never met so extraordinary a combination of sounds, and I could form no conclusion but that the pericardium contained air in addition to an effusion of serum and coagulable lymph."

This splashing, churning sound was described in 19 of the cases. In 24 there was loud metallic tinkling, synchronous with the heart sounds. In 16 cases these noises could be heard at a distance from the patient, and in many instances patients themselves were conscious of the unusual tumult going on in the chest.

In only 6 cases was the presence of pneumopericardium first recognized at autopsy.

It speaks strongly for the uniqueness of the acoustic phenomenon that the nature of the trouble should have so often been readily recognized by observers who were meeting it for the first time.

Of the 38 cases 26 resulted fataly, 11 recovered. Among those that recovered 4 were caused by stab wounds, 4 by some injury such as a fall, blow or crush, which produced pneumopericardium without an external perforation, but presumably through a tear of the pericardium itself.

The large percentage of recoveries speaks for the resistance to injury which this membrane is capable of exhibiting.

No.	Reporter.	Cause.	Physical signs.	Result.	Autopsy.
1	Bricheteau,	Blow upon sternum.	Precordial tympany, splashing sounds, "bruit de moulin" heard at distance.	Died.	Yes.
2	Trotter,	Ulcer of esophagus perforating into pericardium.	Not recognized during life.	Died.	Yes.
3	Chambers,	Ulceration of esophagus communicating with pericardium.	Not recognized during life.	Died.	Yes.
4	Feine,	Traumatic.	Precordial tympany, shifting with position; faint metallic sound with heart beat.		
5	Stokes,	Acute pericarditis.	Cracked-pot resonance, gurgling sounds synchronous with heart beats.	Recovered.	
6	McDowel,	Tuberculosis of lungs, ulcerating into pericardium.	Clear percussion note, metallic tinkling, splashing synchronous with heart beat.	Died.	Yes.
7	Buist,	Wound of esophagus from swallowing false-tooth plate.	Case not recognized during life.	Died.	Yes.
8	Flint,	Knife stab wound.	Splashing sound.	Recovered.	
9	Tuettel,	Cancer of esophagus ulcerated into pericardium.	Metallic murmur, splashing heard at a distance from bed.	Died.	Yes.
10	Begbee,	Cancer of esophagus perforating into pericardium.	Precordial tympany; splashing, churning sounds heard at distance.	Died.	Yes.
11	Graves,	Abscess of liver perforating into pericardium.	Metallic click synchronous with heart sounds.	Died.	Yes.
12	Morel-Lavallee,	Fall, multiple severe injuries.	Loud splashing metallic sounds.	Died.	Yes.
13	Morel-Lavallee,	Fall, fracture clavicle, rupture pericardium.	Loud splashing metallic sounds heard at a distance.	.....	Yes.
14	Morel-Lavallee,	Kicked by horse, fracture 4th, 5th, 6th, and 7th ribs.	Loud splashing, churning sounds heard at a distance.	Recovered.	
15	Bodenheimer,	Bullet wound below left nipple; suicide.	Tympany, metallic tinkle with heart sounds.	Died.	Yes.
16	Saexinger,	Perforation of ulcer of stomach into pericardium.	Precordial tympany, metallic splashing murmur at distance.	Died.	Yes.
17	Gruttner,	Stab wound over heart.	No signs noticed.	Died.	Yes.
18	Friedreich,	Difficult labor, pleurisy, empyema; no perforation.	Precordial tympany, metallic heart sounds heard at distance.	Died.	Yes.
19	Steiger,	Fall, fracture of arm, shoulder and ribs.	Precordial tympany, splashing, metallic heart sounds heard at distance.	Recovered.	
20	Dolbeau,	Stab wound.	Precordial tympany, amphoric bruit with metallic sounds.	Died.	Yes.
21	Walshe,	Wound of esophagus from swallowing sword.	Precordium tympanitic, no gurgling or succussion; sounds not very loud.	Died.	Yes.
22	Eisenlohr,	Pyopneumothorax perforating into pericardium.	Tympany over precordium, metallic and musical; loud splashing murmur heard at distance.	Died.	Yes.
23	Fetzer,	Bullet wound of shoulder, suppuration, arthritis; no perforation of pericardium.	Precordial tympany, musical heart sounds heard at distance.	Died.	Yes.
24	Meigs,	Small ulcer of esophagus perforating into pericardium.	Precordial tympany; splashing, churning sound heard at distance; metallic tinkle.	Died.	Yes.
25	Müller,	Purulent pericarditis perforating into the bronchus with discharge.	Ringing, metallic heart sounds with percussion.	Recovered.	
26	Müller,	Crush of thorax with fracture of clavicles and ribs; tear of lungs.	Tympany over precordium; metallic resounding murmur with heart sounds.	Recovered.	

No.	Reporter.	Cause.	Physical signs.	Result.	Autopsy.
27	Müller,	Stab wound of chest.	Tympany over heart; loud metallic, ringing murmur, and succussion synchronous with heart.	Recovered.	
28	Aran,	Paracentesis of pericardium.	Tympany, succussion, bruit de moulin.	Recovered.	
29	Guttman,	Ulcer of stomach perforating into pericardium.	Precordial tympany and loud metallic heart sounds heard at distance.	Died.	Yes.
30	Audry,	Stab wound of pericardium.	Precordial tympany, splashing sounds, metallic tinkle.	Recovered.	
31	Leonpacher,	Fall upon back.	Precordial tympany, musical heart sounds heard three feet from bed.	Recovered.	
32	Combemale,	Perforation of tubercular cavity of lung into pericardium.	No signs noted.	Died.	Yes.
33	Nichols,	Appendicitis, empyema, pyopneumopericardium, no perforation supposed bacillus aerogenes.	Metallic tinkling and splashing sounds heard at distance.	Died.	Yes.
34	Laub,	Sore throat and facial erysipelas.	Precordial tympany above, dulness below shifting with position, low metallic splashing heard at distance.	Recovered.	
35	Pelcz,	Tubercular abscess between esophagus and pericardium and communicating with both.	Not discovered till autopsy.	Died.	Yes.
36	Sievers,	Gangrene of left lung perforating into left pleura and then into pericardium.	Loud splashing and metallic sounds.	Died.	Yes.
37	Huber,	Ulceration of necrotic lymph node into esophagus and pericardium.	Precordial tympany, metallic dripping sounds.	Died.	Yes.
38	James,	Perforating wound of esophagus by sliver of bone.	Shifting dulness and tympany; splashing, churning sounds and musical tinkle heard at a distance.	Died.	Yes.

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THREE CASES OF PROBABLE PSITTACOSIS.

By HERMAN F. VICKERY, M.D.,
OF BOSTON.

WITH BACTERIOLOGIC REPORT.

By OSCAR RICHARDSON, M.D.,
OF BOSTON.

In 1879 J. Ritter[1] reported a house epidemic of severe pneumonia which he ascribed to contagion from parrots, or rather the cages in which the birds had been transported. Similar observations were made by Ost[2] in Berne in 1882 and Wagner[3] in Leipzig in 1882 and 1886.

In December, 1891, 500 parrots were purchased in Buenos Ayres for the Paris market. Of these 300 died on the voyage and 200 reached Paris in February, 1892. During that year there were 49 cases of the disease now known as psittacosis, ascribed to infection from these parrots, with 16 deaths. In 1893, 7 cases with 5 deaths; in 1894, 2 cases, both of which recovered; in 1895–96, 12 cases, with 3 deaths.

In 1894–95 there were house epidemics in Florence and Ponto of a malignant atypical pneumonia, appearing almost simultaneously in several members of the same family or even involving the whole family, and in some instances conveyed directly from one individual to another. This visitation was ascribed to parrots which had been imported by way of Genoa from South America. Observations[4] were made by Banti, Malenchini and Palamidessi.[5]

In 1897 it was reported[6] that in Genoa 14 persons fell sick and 8 died because of two parrots brought from Brazil.

In 1898 in the Julian Venetia 3 inmates of one house fell sick, and of these 2 died, where 2 parrots had died shortly before. Leichtenstern[4] observed house epidemics in Cologne in 1898. In one

there were 10 cases and 4 deaths; in a second 8 cases with 1 death. Leichtenstern regards it as probable, but not susceptible of absolute proof, that both these groups of cases were referable to contagion from parrots.

In 1880 Eberth[4] reported the discovery of enormous numbers of micrococci in the body of a gray parrot, and in 1883 M. Wolff[8] examined the bodies of 12 gray parrots from the Guinea coast with a view to explaining the immense mortality in parrots brought thence to Germany. He also found micrococci in great numbers.

In 1893 Nocard[9] isolated a specific bacillus belonging to the group of colon bacilli.

Among the Florentine casés Palamidessi (already mentioned), in a house epidemic which attacked five persons in one family a few days after a South American parrot was introduced, found a microbe similar to the bacillus of chicken cholera, but more like Nocard's bacillus, though apparently not identical with it.

In 1896 Gilbert and Fournier[10] reported 5 cases of psittacosis in man; of these 2 died. In the heart's blood of one Nocard's bacillus was found *postmortem*. It proved to be an extremely virulent organism, killing rabbits, mice and pigeons within fourteen to eighteen hours after inoculation.

Nicolle[11] reported, in 1899, an epidemic affecting 8 persons, of whom 4 died. Although he did not find Nocard's bacillus, he obtained a serum agglutination from a culture of that bacillus in dilutions of 1:50 and 1:60. The serum also caused a clumping of typhoid bacilli, although the patient had never suffered from typhoid fever; but Widal[12] and Sicard[4] (1896) claimed that they could differentiate the typhoid bacillus from Nocard's by the serum reaction.

The symptoms of the disease in parrots are: loss of appetite, debility, drooping of the wings and diarrhea, ending with convulsions and death. In man the symptoms of the Paris epidemic might be summarized as those of a grave typhoidal condition, with atypic pneumonia. The onset is acute, often with chilliness or a true rigor. Exceptionally the disease begins insidiously, but in that case there is apt to be a chill when the pneumonia begins. The temperature is often 103° on the first day and perhaps 104° on the second day of the illness. The fever is more or less continuous, with a termination by lysis. In many cases successive foci of pneumonia develop, giving the temperature curve a recurrent type.

With the onset the patient is feeble and depressed; he usually has a violent headache and is often dizzy. There may be delirium. As a rule there is obstinate constipation, but some cases suffer from diarrhea. The spleen is always enlarged; there may be a roseolar eruption or petechiæ. From the beginning of the disease there is a noticeable cough, and on auscultation subcrepitant rales are found throughout both lungs; then after a few days there is a slow development of pneumonia, which may be either lobular or lobar. In some cases, however, there may be no evidence of consolidation.

In the cases reported by Leichtenstern, above referred to, the illness was similar. There was the greatest weakness and depression from the start and almost invariably a severe headache, but no cases had delirium. As a rule, there were no abdominal symptoms. The spleen was not found to be enlarged in any of the cases, thus contrasting with the Paris epidemic.

The period of incubation varied from one to three weeks in the Paris and Cologne epidemics. Warthin states that it is from seven to twelve days. The mortality is put at 37 per cent. The disease is said to be more severe in the elderly. Treatment is purely symptomatic.

Czaplewski made bacteriologic investigations in Leichtenstern's cases. He sums up as follows: 1. The parrot which he examined did not die of infection from Nocard's bacillus. 2. No conceivable etiologic connection can be proved between the disease of the parrot and the illness of those in whose house it was. He adds that he does not at all wish to deny the possibility of the existence of a genuine infectious disease in parrots communicable to man.

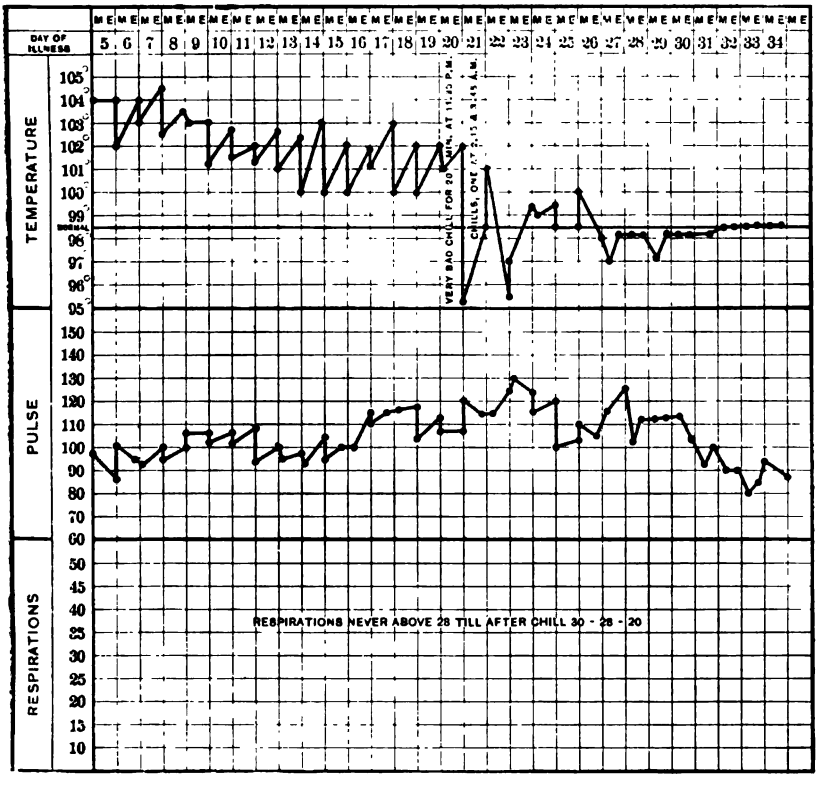
As Warthin states, "the bacteriology of psittacosis and the true relations of the parrot disease to the atypic pneumonia seen in man are yet to be definitely determined."

This outline of our knowledge as to psittacosis may be convenient for comparison with three cases of disease which came somewhat under my own observation in Wolfboro, Carroll County, New Hampshire, in December, 1903. They were the patients of Dr. Nathaniel H. Scott, and were seen by me in consultation with him and Dr. Stillman P. Getchell, both of Wolfboro. No similar cases preceded or followed those about to be reported, which affected three out of the four members of one household.

Mr. and Mrs. M. visited New York City in November, 1903, and while there they sent home to Wolfboro a green parrot, which

arrived November 7th. They returned one week later. The parrot had a bloody diarrhea and died November 21st. It was kept in the sitting-room occupied by Mr. and Mrs. M. and was cared for especially by their domestic, Mrs. J., and somewhat by Mrs. M. The fourth member of the household was Mr. J., the husband of the

CHART I.


DAY OF ILLNESS
5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34
TEMPERATURE
PULSE
RESPIRATIONS
VERY BAD CHILL FOR 20 MIN. AT 11:20 P.M.
CHILLS, ONE AT 7:15 & 8:10 A.M.
RESPIRATIONS NEVER ABOVE 28 TILL AFTER CHILL 30 - 28 - 20

CASE II. MR. M.

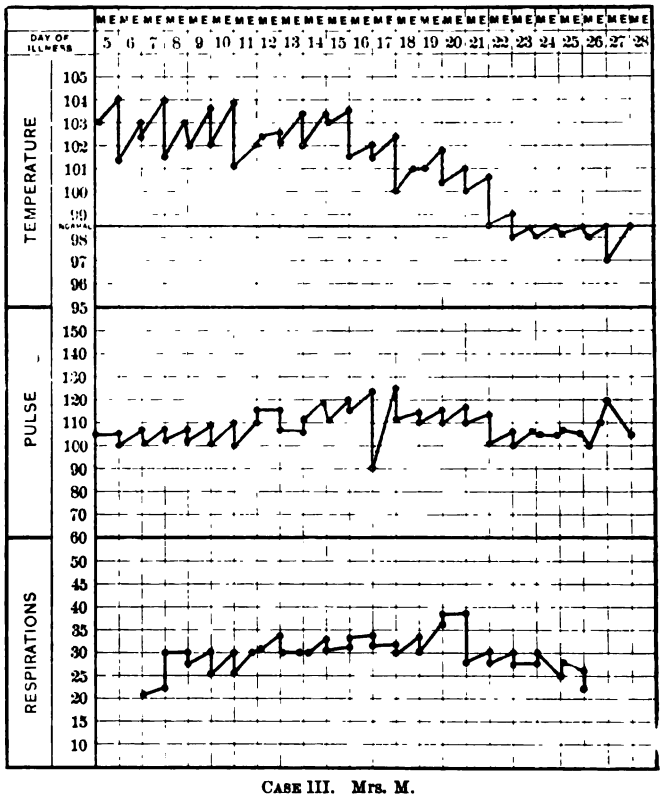
domestic; but Mr. J.'s work kept him throughout the day away from home, while the head of the house, Mr. M., spent much time in the room where the parrot was.

CASE I.—Mrs. J., a young woman of previous good health, was taken ill suddenly November 25th, eighteen days after the parrot arrived and four days

after it died, with prostration, pain in the right scapula, a temperature of from 102° to 103°, vomiting and constipation. The temperature was about 103° for a week, then was normal three or four days and rose again, remaining elevated for a week, and finally terminating by lysis, with the slow recovery of the patient. There was no cough.

CASE II.—Mr. M., aged sixty-two years, had once a severe attack of typhoid. His habits and general health were good; but eight years ago he suffered severely

CHART II.



CASE III. Mrs. M.

from prostatic trouble, complicated by an abscess in the scrotum, which caused destruction of both testicles and was followed by apparent atrophy of the prostate gland, with considerable relief of the bladder symptoms. For some days previous to his present illness he had seemed languid. On November 29th he was obliged to go to bed, with a temperature of between 103° and 104° and a pulse of about 100. He was first seen by me December 11th, when his tem-

perature was 103° in the afternoon, with a pulse of 104 and a condition, according to Dr. Scott, much more favorable than some days before. The leukocyte count was 8640. The tongue was rather dry, but clean. The respirations were about 28 per minute, and there were no marked pulmonary symptoms. The walls of the radial arteries seemed calcified and the aortic second sound was accented.

When seen by me again on December 16th the white count was 5780. There were moist rales in both bases, especially posteriorly, with slight dulness and diminished respiration in the lower part of the axilla and back, on the right side; but no bronchial respiration could be detected. The throat contained a thick, viscid and almost membranous secretion. He had been rather worse since December 11th. He was somnolent and had Cheyne-Stokes respiration.

On December 23d he was again seen by me and seemed to be slowly improving, but on the 17th he had had a severe chill, with great prostration, and on the 18th two similar attacks. These, however, seemed to be referable to cystitis, with offensive, purulent urine, which improved upon the administration of urotropin, with gradual and permanent convalescence.

CASE III.—Mrs. M., aged sixty-seven years, had a family history of apoplexy and diabetes. The patient had been growing old rapidly in the last two years. She fell ill November 27th, and was seen by me December 11th. There was high fever and delirium, with constipation. The leukocyte count was 13,200. The pulse was 120 per minute, and Dr. Scott stated that it had been growing progressively weak and rapid. The chest was full of moist rales, which in some places seemed high-pitched, but no distinct consolidation could be made out. The abdomen was soft; no enlargement of spleen or liver could be detected either in her case or that of her husband. Within a day or two her condition became still worse, but it was improved by a purge and by the injection of normal saline solution with adrenalin.

On December 16th the white cells numbered 8960. There was a white deposit in the mouth and throat which proved to be thrush. While moist rales could still be heard in both lungs; they were fewer than five days previously, and now coarse, dry rales were audible. The heart was stronger. From this time she improved quite rapidly. On December 11th and December 16th the Widal test proved absolutely negative in both Case II. and Case III. On December 16th paratyphoid and paracolon tests were likewise negative.

The general aspect of the cases should be mentioned. It was well described by Dr. Scott and Dr. Getchell, when I first had the honor of meeting them, as being more like typhoid than anything with which they were familiar, but yet probably not typhoid fever. Temperature charts of both Mr. and Mrs. M. accompany this report. No eruptions developed in either of the cases.

With regard to the etiology. As has been said, no similar cases

existed in the village. The sanitary condition of the house had been brought into question. It occupied an elevated and healthful location, but the plumbing was defective. The pipe leading from the kitchen sink to the cesspool, into which all the waste material of the house was drained, had no trap, and, furthermore, it did not reach to the surface of the water in the cesspool, so that there was a free access of the air from the cesspool into the kitchen; but there had been no change in the plumbing for three years, and for months a peculiar smell had been noticed occasionally in the kitchen.

Conditions such as these are highly undesirable, and they do promote illness by depressing the general condition of the occupants of the house and rendering them vulnerable to specific infectious agents; but it seems unlikely that they can account for so explosive an outbreak in persons for several years accustomed to them.

If Mr. and Mrs. M. brought some infection with them from New York, it is difficult to explain why the domestic fell ill before they did. Moreover, influenza, the likeliest disease to be considered, has usually an incubation period of two or three days, while they returned eleven days before the first illness occurred.

The advent and demise of the parrot were not known to me until my second visit, December 16th. I then invited the co-operation of my friend, Dr. Oscar Richardson, assistant in the Clinicopathologic Department of the Massachusetts General Hospital, and his report is as follows:

Bacteriologic Report.

At the request of Dr. Vickery, I made, in December, 1903, examinations of blood taken from the cases which are described in his paper.

The blood examined came from Mr. J. H. M. and Mrs. J. H. M., and was subjected to the following agglutination tests: The blood from each case was added to bouillon cultures, twenty-four hours old, of a known typhoid bacillus and a known paratyphoid bacillus, in the proportions of one of blood to ten of culture, and observed for half an hour. On the expiration of the time of observation all the tests were found to be so definitely negative that higher dilutions were not made.

A short time later more blood from each case was obtained and further tests made with different strains of typhoid bacilli and bacilli of the paratyphoid-colon group, but all the tests were negative.

Finally, an agglutination test was made with a bouillon culture of a streptococcus-like micro-organism recovered from the spleen of the parrot associated

with the cases under consideration, but this test, like the others, gave no evidence of any reaction.

Stained cover-glasses of the blood were also made and examined, but no malarial organisms were found, and the blood showed nothing worthy of note, except for a slight increase in the number of leukocytes. Cultures were made from the throats of these cases, but the growths obtained showed nothing unusual.

At the time when the cases under consideration were taken ill they had in their household a sick parrot, which finally died and was buried. As soon as this fact was learned by Dr. Vickery the parrot was exhumed, packed in a box and sent to the laboratory, where it was received on December 21, 1903. The bird had been buried for about a month.

At the autopsy, which was held immediately, the body of the bird gave forth no marked odor and outwardly showed nothing worthy of note. On section the viscera presented no demonstrable lesions, and the postmortem changes, which were well marked in the intestines, were not apparently so far advanced in the solid organs. The brain was not remarkable.

Cover-glasses were made from the heart blood, liver, spleen and the marrow of the wing bones and stained with Loeffler's blue and Wright's blood stain, but on examination no bacteria or other micro-organisms were found.

Aerobic and anaerobic cultures were made on blood serum from the following sources: heart blood, liver, spleen, the marrow of the wing bones and the brain. After forty-eight hours in the incubator at 37° C. the cultures showed no visible growth, with the exception of the aerobic culture from the spleen. This culture showed on the surface of the medium one small, round, gray-white colony and its water of condensation had a slightly cloudy appearance.

Microscopic examination of the cultures showed that no bacteria were present in any of them, except in the aerobic culture from the spleen. The single colony in this culture was found to be a micrococcus morphologically and culturally like the streptococcus. The water of condensation of the culture from the spleen was found to contain a similar organism to that in the colony.

A guinea-pig was inoculated from a twenty-four-hour-old subculture in bouillon from the colony, but the animal remained unaffected after many days.

This streptococcus-like micro-organism found in the culture from the spleen is, therefore, regarded as having no etiologic relation with the unknown cause of death of the parrot, and it is probably a contamination.

It is to be regretted that an examination of the parrot could not have been made about the time of its death, as it seems quite probable that by cultures and cover-glasses made then, any bacterium that might have been the cause of the possible infection of the bird would have been discovered.

These negative results of the various tests and examinations recorded above are disappointing, but they are of considerable importance in ruling out those diseases the atypic forms of which psittacosis resembles.

To sum up, three occupants of one house are taken ill almost simultaneously and two nearly die of a disease corresponding fairly well to the descriptions of psittacosis and not easily placed in any other category. The time elapsing after the arrival of the suspected parrot corresponds to the period of incubation in psittacosis. The milder attack of the young patient is according to the rule. The only member of the household who escapes illness has had little to do with the parrot, but is the husband of one of the patients.

A personal visit to the dealer in New York from whom the parrot was purchased had no satisfactory result. In another shop which obtains its parrots from the same wholesale house, I learned that three employés had been ill this spring, two with pneumonia and one with "la grippe."

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A STUDY OF THE TUBERCLE BACILLI ISOLATED FROM THREE CASES OF TUBERCULOSIS OF THE MESENTERIC LYMPH NODES.

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GEORGE FABYAN PROFESSOR OF COMPARATIVE PATHOLOGY, HARVARD UNIVERSITY.

THE desirability of studying tubercle bacilli from those cases of tuberculosis which are presumably the result of food infection was emphasized by me[1] in 1898 as the surest way of gaining an insight into the relation between bovine and human tuberculosis. In a more recent contribution[2] I described among other cultures two from the mesenteric glands of children, one of which (Human XI.) was pronounced to be of bovine origin. At the same time I supplemented the studies made by Ravenel upon a presumably bovine culture (BB) from a child by applying a new reaction test there described for the first time. This latter culture had also the characteristics belonging to the bovine bacillus.

I shall not attempt to review certain articles which have appeared since the conclusion of the manuscript of my former communication in May, 1903, since they do not bear directly upon the contents of this paper, but simply begin with the statement that no observations have thus far been presented which invalidate the distinction between the bovine and the human race or variety of tubercle bacilli made by me in 1898. This distinction, as I then clearly stated, does not imply that the bovine bacilli, under certain conditions, might not invade the human subject.

In the following pages three cultures, all of them from the mesenteric lymph nodes of human beings, are studied from those points of view best adapted to inform us whether they are of the bovine or of the human variety.

[1] Journal of Experimental Medicine, 1898, vol. iii. p. 451.
[2] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, 1903, vol. xviii. pp. 109–151.

HUMAN CULTURE XIII.

For the material from which this culture was isolated I am indebted to Prof. Mallory and to Dr. H. A. Christian, who performed the autopsy, from the protocol of which extracts are given below.

The case was that of an infant, eight months old, in the service of Dr. T. M. Rotch, at the Children's Hospital, Boston, Massachusetts. The clinical history may be very briefly summarized.

About three months before admission the child began to have swelling of glands on the left side of neck and face. These have been opened, but they have recurred again and again. There has been coryza for two months, which has interfered with nursing. The lesion of the neck was incised, the pus pressed out and proper treatment instituted. There was no positive reaction from two injections of tuberculin given on the seventh and the ninth days. The child died on the fourteenth day after admission. The autopsy, performed fifty-four hours postmortem, brought out the following pathologic conditions:

"There was pneumonia in both lungs, but no evidence of tuberculosis in any of the organs of the thorax.

"In the abdomen the mesenteric lymph nodes are enlarged and many of them soft and cheesy. In the spleen there are miliary tubercles.

"In the ileum, close to the ileocecal valve, there is a small yellowish nodule which projects slightly into the lumen of the intestine. The mucous membrane over this is intact, and the size of the nodule does not exceed 4 mm. In the ascending colon there is a somewhat similar lesion a little larger and over the surface of which the mucosa is slightly ulcerated and somewhat pigmented. With the exception of these two lesions the intestinal tract was normal.

"Liver, weight 310 grams. The surface is a pale tawny pink, and scattered over it are numereus nodules from 3 to 5 mm. in diameter, which are lighter in color. Some of these project considerably above the surface of the liver, others project but slightly. Just at the periphery of each there is a slight depression in the liver, giving the areas a somewhat button-like appearance. On the cut surface these nodules are yellowish or grayish in color, and many of them can be made out to be formed of smaller coalesced areas of similar character. On the surface of the liver some similar nodules are seen always near the surface, and, as a rule, extending to the surface of the liver. In the tissue about some of the bloodvessels a few small grayish points, probably miliary tubercles, can be made out.

"Throughout the meninges can be seen a few, generally widely separated and very small, grayish areas. In a few places these become much more numerous and more closely set. This is particularly true of the adjacent surface of the posterior portion of the longitudinal fissure and the superior median surface of the cerebellum. This is also true of the surface of the island of Reil, in which, on both sides, there is a conglomerate tubercle fully

1 cm. in diameter, firm, of a yellowish color, and closely adherent to the surface of the cortex, though apparently not embedded in it. Over the base of the brain, particularly along the surface of the medulla, pons and basal ganglia, there is a moderate amount of yellowish fibrinous exudate. This is also present over the anterior portions of the temporal lobes, and here appears to have a more purulent character. . . . ."

The anatomic diagnosis includes tuberculous, exudative and miliary meningitis, conglomerate tubercle in the island of Reil on both sides, tuberculous nodules in intestine, caseous tuberculosis of mesenteric lymph nodes, conglomerate tuberculosis of liver and miliary tuberculosis of spleen.

The culture was obtained from one of the mesenteric lymph nodes. These were about 1 cm. in diameter, centrally soft, caseous. In several smears tubercle bacilli were not found. A dense suspension of caseous material in normal salt solution was injected into the abdomen of three guinea-pigs. Cultures were obtained on dog serum, horse serum or egg medium from all of the guinea-pigs. The growth and appearance in all the tubes indicated identity. In all cases the development was prompt and vigorous, indicative of the human race of bacilli. The growths became heavy, coalescing, smooth or wrinkled membranes. In some cases well-isolated, smooth, roundish colonies were obtained. Good growth on glycerin agar followed the inoculation of subcultures. In the earliest cultures the bacilli appeared as solid rods, of somewhat variable length, measuring from 1 to 2.2 μ in length. In somewhat later cultures they were so irregular and polymorphic in outline that measurement was impossible. The preliminary inoculation of guinea-pigs with tissue had already indicated bacilli of a low degree of virulence. The subsequent tests upon rabbits and guinea-pigs with definite suspensions of pure cultures confirmed the early inference. In Table I. the results of tests upon rabbits and in Table II. those on guinea-pigs are given. In both species marked resistance to this bacillus is manifest.

That it is not an attenuated or modified bovine culture is made evident by the culture reactions given in Table III. For the sake of comparison a bovine culture was included in each group of cultures. In all three tests the difference between the bovine and the human races is in evidence.

HUMAN CULTURE XIV.

This bacillus was isolated from material obtained through Professor Mallory. The patient, a Chinaman, twenty-six years old, was

admitted to the Boston City Hospital suffering from nausea and pain in the stomach. Physical examination revealed nothing unusual.

During his stay in the hospital the temperature fluctuated between normal and 104°. Rales developed in both lungs, which gradually increased in intensity, although no definite consolidation could be detected. The patient died on the sixteenth day after admission, after a gradual failure of heart and respiration. From the autopsy protocol of Dr. Mallory the following points are of interest to us:

In the peritoneal cavity "surfaces smooth and shiny, with no increase in fluids. Mesenteric lymph nodes much enlarged. One of the glands measured 2 cm. diameter; glands were confluent. On section there was revealed a yellowish, cream-cheese-like substance; a smear from the same reveals B. tuberculosis . . .

"Pleural cavity. Left lung bound everywhere by rather strong fibrous adhesions. On separating the costal and parietal pleura many minute, grayish, raised areas are seen.

"Lungs. Dark-red, hubbly surface, non-crepitant throughout, except for a few subcrepitant areas at the apices. On section surface is dark red, rather dry, and scattered everywhere are grayish-white areas, averaging 2 to 3 mm. in diameter, discrete, often confluent. Bronchial lymph nodes not enlarged. Bronchi filled with mucopurulent material . . .

"Kidneys. . . . Scattered throughout cortex and in pyramidal region are a number of yellowish-gray areas not raised above the surface, averaging 2 mm. diameter, discrete for most part, occasionally confluent."

The anatomic diagnosis included miliary tuberculosis of the lungs and kidney, tuberculosis of the mesenteric lymph nodes and acute tuberculous pleuritis. In this case the evidence obtained from the postmortem examination suggested primary tuberculosis of the mesenteric glands which furnished the infection for the fatal miliary tuberculosis.

The source of the culture studied was a mesenteric lymph node about as large as a horse-chestnut. It was almost wholly converted into a soft caseous mass. In several smears bacilli were not detected. The isolation was made as in the preceding case by injecting a suspension of the cheesy matter into the peritoneal cavity of three guinea-pigs. The disease in the guinea-pigs was so slight that they all greatly increased in weight during the six weeks following the inoculation. In one, chloroformed after ten weeks, no lesions could be found and no cultures were attempted. In the remaining two the

lesions were characteristic, though slight, and nearly all cultures made developed rich crops of colonies, isolated and confluent. Only the cultures from one guinea-pig were tested on animals and in bouillon cultures for the reaction curve.

The bacilli were slightly curved rods, 1.5 to 2.5μ long, the greater number being about 2μ in length. Cultivation on glycerin agar, glycerinized potato and horse serum yielded cultures quite vigorous, although they did not equal in richness those on dog serum.

One rabbit (Table I.) which received twice the standard dose was chloroformed after one month because suffering with snuffles or rhinitis. The lesions found were very slight. The second rabbit, which received the usual dose, was also affected very slightly. The guinea-pig receiving the usual dose had but slight lesions after fifty-eight days. The one receiving twice the usual dose died in eighteen days.

HUMAN CULTURE XV.

The material from which this culture was isolated was sent to me by Dr. Warfield T. Longcope, of Philadelphia, at the suggestion of Dr. Simon Flexner. The case was that of a negro cook, aged thirty-nine, admitted to the Pennsylvania Hospital April 26, 1903. He had been taken ill with cough about two weeks before admission. Of the results of the clinical examination only the following points need be mentioned: Fine crepitations and rhonchi over the lungs; heavy precipitate of albumin in the urine; sputum free from tubercle bacilli. Death ensued on the eighth day. During the disease the temperature was elevated and irregular, ranging from 101° to 104°.

The following abstract of the autopsy protocol was kindly forwarded to me by Dr. Longcope:

Anatomic Diagnosis. Acute disseminated miliary tuberculosis, caseation of mesenteric lymph glands, tuberculosis of lateral ventricles of brain, tuberculosis of thoracic duct, acute splenic tumor, cloudy swelling of liver and kidneys, acute aortic endocarditis.

Peritoneal cavity normal. Pleural surface covered with miliary tubercles. Pericardium normal.

Heart. On two of the cusps of aortic valves there are several delicate gray and yellow granular vegetations which are distributed along the point of closure of the valves beneath the vela. The aortic as well as the other valves are thin and delicate. No other marked changes in heart.

Lungs. Slight chronic fibrous pleurisy; pleura everywhere sanded with minute miliary tubercles. On section the cut surface of both lungs is seeded

with small gray and yellow tubercles. Very few exceed pinhead in size, but some in upper lobe of left lung are caseous and are 2 to 4 mm. in diameter. There are no cavities, old scarred areas or evidence of chronic tuberculosis.

Spleen. Weight, 170 grams. It is filled with miliary tubercles.

Liver. Cut section seeded with fine pinpoint gray tubercles.

Kidneys. Many tubercles scattered over capsule and cut sections. They are gray and yellow and measure from 2 to 3 mm. in diameter.

Pelvis and ureters normal. No lesions found in stomach, *intestines*, urinary bladder, prostate, seminal vesicles or testes.

Mesenteric glands average 2 to 3 cm. in diameter. Most of them are either entirely caseous or contain large areas of caseation. Retroperitoneal glands are enlarged, but show no caseation. Thoracic duct thickened throughout. Near the receptaculum chyli the lumen is partially filled with soft caseous material. The walls of the duct are everywhere studded with gray or yellow tubercles.

In this case, as in the preceding one, the evidence that the tubercle bacilli entered by way of the intestines was pretty definite, and hence an effort was made to isolate the bacillus. The material sent to me was a piece of lung tissue. It contained, besides many tubercle bacilli, a variety of other bacteria. Three guinea-pigs receiving intraperitoneal injections of salt solution in which the lung tissue had been torn up died within twelve hours. An effort was next made to remove the miscellaneous bacteria by washing the remaining tissue repeatedly in sterile salt solution. After this treatment stained preparations of the tissue showed only a very large number of tubercle bacilli. These were either straight or slightly bent rods fully 4μ long. A few were fragmented.

A second lot of guinea-pigs were inoculated with the washed tissue, two into subcutaneous pockets with bits of tissue, a third with a suspension into the peritoneal cavity. All remained alive until chloroformed after twenty-five to thirty-five days. The disease ran a mild course, and when chloroformed all the guinea-pigs had gained considerably in weight. Successful cultures were obtained from each guinea-pig. The bacilli grew in the form of large isolated or confluent colonies of a smooth, glistening appearance on dog's serum. Subcultures on glycerin agar and in glycerin bouillon were readily obtained and after several generations the appearance of the cultures differed nowise from the human type of bacilli.

In form they varied in length from 1 to 3μ, the greater number being 1.5 to 2μ long, slightly curved.

For the virulence and culture tests two strains from two different guinea-pigs, denominated respectively XVa. and XVc., were saved. The effect of this tubercle bacillus in pure culture, even in twice the doses usually given, was that of a highly attenuated type, as shown in Tables I. and II. It will be noticed that one guinea-pig was pregnant at the time of inoculation. This condition, unknown at the time, was probably the cause of the early death as compared with the mate inoculated with the other strain of bacilli. The second animal lived a long time in spite of the fact that the inoculation was intra-abdominal.

In the rabbits the disease was very mild and the lesions limited to a few foci in the kidneys of both and a few translucent tubercles in the lungs of one. The one receiving 1½ times the standard dose gained nearly 500 grams in three months.

THE REACTION TEST IN GLYCERIN BOUILLON.

In a preceding paper[1] the writer called attention to the difference in the movement of the reaction of the glycerin bouillon in which bovine and human bacilli are multiplying. In the case of the bovine cultures this movement leads to a final reaction, either neutral, feebly alkaline or feebly acid, toward phenolphthalein, in case of the human cultures to a pronounced acidity to phenolphthalein. In the latter the reaction at first becomes less acid, then either much more acid or else it remains at a medium level. Concerning various precautionary details in applying this test to cultures, the reader is referred to the earlier paper.

In Table III. the tests made with the three new cultures are given in detail. Three different lots of glycerin bouillon were tried, and for controls two older cultures (Bovine VIII. and Human XII.) were studied side by side with the new ones.

The first lot of glycerin bouillon, No. 1111, was, for some unknown reason, opposed to a very active growth of the bacilli. The membranes remained thin and smooth, and as a result the alkali production in Bovine VIII. was feeble and inhibited after a time. This case, the first I have encountered, suggests caution in interpreting results until several lots of bouillon have been tried.

[1] TRANSACTIONS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, 1903.

TABLE I.—RABBITS. (All inoculations are into an ear vein.)

Designation of culture.	Total age of culture.	No. of transfer.	Age of culture used.	Dose in c.c.[1]	No. of rabbit.	Date of inoculation.	Initial weight (grams)	Final weight (grams)	Result.	Remarks.
Human XIII.	28 days.	Second	10 days	1.00	104	Apr. 25, 1908	2970	2992	Chloroformed after 2 months.	Very fat; foci in kidneys; barely visible tubercles in liver; lungs free.
" XIII.	28 "	Second	10 "	0.5	171	Apr. 25, 1908	1648	1870	Chloroformed after 2 months.	A few foci in kidneys; some minute tubercles in lungs.
" XIV.	35 "	Second	9 "	1.00	138	May 2, 1908	2548	1995	Chloroformed after 1 month.	Because of discharge from nostrils ("snuffles"); considerable number of small tubercles in kidneys; a few minute tubercles in lungs.
" XIV.	35 "	Second	9 "	0.5	172	May 2, 1908	1625	1540	Chloroformed after 54 days.	Many foci in kidneys; none in lungs; tubercles in iris of both eyes.
" XVa.	3 months 18 days.	Fourth	10 "	0.75	132	Oct. 3, 1908	1990	2455	Chloroformed after 3 mos. 12 days.	Moderate number of foci in kidneys; none in lungs.
" XVc.	3 months 8 days.	Third	10 "	0.4	180	Oct. 3, 1908	1975	2245	Chloroformed after 2 mos. 4 days.	A very few gray tubercles in kidneys and lungs.

[1] The suspension in normal salt solution is, as heretofore, equivalent in density to a twenty-four-hour bouillon culture of typhoid bacilli after removal of clumps by sedimentation. Dog serum was the culture medium.

TABLE II.—GUINEA-PIGS. (All inoculations are intra-abdominal.)

Designation of culture.	Total age of culture.	No. of transfer.	Age of culture used.	Date of inoculation.	Dose in c.c.	Initial weight (grams)	Final weight (grams)	Result.	Remarks.
Human XIII.	28 days	Second	10 days	Apr. 25, 1908	1.00	319	234	Died in 52 dys.	Lymph nodes not affected; spleen large; no visible tubercles in lungs, liver and spleen.
" XIII.	28 "	Second	10 "	Apr. 25, 1908	0.5	301	260	Died in 48 dys.	Like preceding.
" XIV.	35 "	Second	9 "	May 2, 1908	1.00	375	300	Died in 18 dys.	Multiple necrotic foci in liver; spleen large; lungs not affected; lymph nodes barely so.
" XIV.	35 "	Second	9 "	May 2, 1908	0.5	379	325	Chloroformed in 58 days.	Spleen large; no visible tubercles in any organ, except on testicles.
" XVa.	3 mos. 18 dys.	Fourth	10 "	Oct. 3, 1908	0.5	397	....	Died in 50 dys.	Lungs filled with tubercles; liver and large spleen free.
" XVc.	3 mos. 8 dys.	Third	10 "	Oct. 3, 1908	0.5	410	270	Died in 18 dys.	Hyperplasia of omentum; multiple necrosis in liver; lungs compressed by effusion; no visible tubercles; pregnancy discovered after inoculation.

TABLE III.

Composition of bouillon.	Designation of culture.	Date of inoculation.	Reaction of bouillon in per cent. of a normal solution after (— = acid, + = alkaline).
No. 1111.[1] One per cent. Witte peptone; three per cent. glycerin. Reaction — 2.05. Moderate amount of muscle sugar.	Bovine VIII.	May 8, 1903	35 days = — 1.05; 48 days = — 0.75; 81 days = — 0,6.
	Human XII.	" 8, "	35 " = — 1.65; 48 " = — 1.6 ; 81 days = — 2.1.
	" XIII.	" 8, "	35 " = — 1.65; 81 " = — 1.45.
	" XIV.	" 8, "	35 " = — 1.6 ; 81 " = — 1.65.
	" XVa.	Sept. 29, " [2]	49 " = — 1.3 ; 85 " = — 1.6.
No. 1132. Same composition as above. Reaction = — 1.8. Trace of muscle sugar only.	Bovine VIII.	June 22, 1903	71 days = — 0.3 ; 94 days = — 0.15.
	Human XII.	" 22, "	71 " = — 1.7 ; 94 " = — 2.25.
	" XIII.	" 22, "	71 " = — 1.15; 94 " = — 1.00.
	" XIV.	" 22, "	71 " = — 1.8 ; 94 " = — 2.1.
	" XVa.	Sept. 29, " [2]	63 " = — 1.2 ; 89 " = — 1.6.
No. 1153. As above. Reaction = — 1.8. Slight amount of muscle sugar.	Bovine VIII.	Sept. 18, 1903	31 days = — 0.25; 60 days = — 0.0 ; 96 days = — 0.0.
	Human XIII.	" 29, "	30 " = — 0.8 ; 62 " = — 6.5 ; 86 " = — 0.75.
	" XIV.	" 18, "	60 " = — 0.85; 99 " = — 1.65.
	" XVa.	" 18, "	53 " = — 1.00; 85 " = — 2.35; 99 " = — 2.45.
	" XVc.	" 29, "	31 " = — 1.00; 63 " = — 2.5 ; 89 " = — 2.85.

[1] This lot of bouillon was unfavorable for some unknown reason, for the membrane of the various cultures remained comparatively feeble. This probably accounts for the cessation of growth of Bovine VIII. before approaching the zero point

[2] These flasks were more or less concentrated by evaporation at the date of inoculation.

The titrations yielded results which agree essentially with those tabulated in the preceding paper. The reaction of the bovine culture in the three lots of bouillon moves gradually to the phenolphthalein neutral point. The human cultures pursue one of two courses. They either attain a greater than the initial acidity after two or three months (Human XII., XIV., XVa. and XVc.) after having become less acid, or else, as in Culture XIII., the reaction remains after some preliminary fluctuation at a medium level of acidity. These changes in reaction have already been discussed and referred to glycerin as the cause. Further investigations on this subject are now in progress.

SUMMARY.

The bacilli isolated from these three cases of presumable food infection do not correspond to the bovine type of bacilli in any one particular.

1. They were readily cultivated from nearly all the guinea-pigs inoculated, and they grew luxuriantly from the start on dog's serum. Subcultures on glycerin agar and glycerin bouillon grew vigorously after the first transfer from dog's serum.

2. Morphologically the bacilli were either fairly long, *i. e.*, they averaged about 2μ in length, or else they were very variable, polymorphic. The uniformly short, straight forms of the bovine type were absent.

3. In all cases the bacilli were of a very low order of virulence, lower even than that of many of the cultures of human origin studied heretofore.

4. None presented the reaction curve of true bovine bacilli.

We have, as yet, no satisfactory evidence concerning the degree of change, if any, which tubercle bacilli of bovine type may undergo in the human body. That changes could be as thoroughgoing as would be the case if we were inclined to attribute these cases of infection by way of the digestive tract to milk is at present quite inconceivable, and we must content ourselves by referring them to infection with bacilli of strictly human origin.

A STUDY OF THE ETIOLOGY OF VARIOLA.

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I. INTRODUCTION.

The prevalence of variola in Cleveland during the past two years afforded us an opportunity to study the disease. A grant of money from the City Council to defray the necessary expenses made it possible to establish a laboratory for this purpose at the Smallpox Hospital.

At the beginning of the work definite plans for the study of the etiology and pathology of the disease were laid out. These embraced, among other things, the study (*a*) of the blood and skin lesions during life and of the blood and organs after death by coverslip preparations and cultures for bacterial and protozoan parasites, which might hold an etiologic relation to the disease; (*b*) of the relation of certain known bacteria, notably streptococcus pyogenes, to variola; (*c*) of the bacteriolytic complements in variola; (*d*) of the agglutinative, hemolytic and endotheliolytic action of the blood serum; (*e*) of the skin and various organs by modern histologic methods for protozoan parasites.

The results (1, 2, 3 and 4) of all but the last section of this work have already been published.

The only part of the published work which immediately concerns us is that all efforts, whether with the microscope or culture media, in test-tubes and plates, or in collodion sacs in the peritoneal

cavity of animals, or inoculations of vesicle material into the anterior chamber of the eye of the rabbit, failed to demonstrate bacteria, visible or invisible with the microscope, which could in any way be considered as having an etiologic relation to the disease.

The failure to grow submicroscopic bacteria under conditions presumably most favorable for their development, the absence of bacteria visible with the microscope, together with the fact that Park and others have shown that the infectious properties of vaccine material are held back by the Berkefeld filter, seem to us to almost conclusively prove that bacteria may be eliminated from consideration.

It is, however, possible that submicroscopic bacteria incapable of growing in the media used, or that bacteria large enough to be seen with the microscope, but not staining with ordinary stains, might be present. The last is so improbable that it may be dismissed.

Our attempts to isolate a bacterium as the cause of variola were negative. We next devoted our attention to the study of the skin and other lesions for protozoa. The results of this study are given in the present paper.

It is a pleasure to acknowledge our indebtedness to Dr. Martin Friedrich, Health Officer of Cleveland, Mr. G. O. Pay and Dr. John A. Sipher for assisting us in getting material. To Dr. W. T. Councilman, of Boston, we are under many obligations for personal communications concerning his own work while in progress and for furnishing us with page proof of the work from his laboratory in advance of its publication.

II. THE RELATION OF PROTOZOA TO THE LESIONS OF VARIOLA AND VACCINIA.

An extensive review of the older literature on this subject is unnecessary, as this has recently been done by Councilman, Magrath and Brinckerhoff. It is sufficient to state that Guarnieri,[5] in 1892, was the first to give accurate descriptions of protozoa-like bodies in the skin lesions of these diseases. His observations and interpretations have been upheld by some workers and disputed by

others. The most convincing work until that of Councilman and his coworkers was published by Wasielewski[6] in 1901. Up to this time no definite life cycle had been established. In April, 1903, Councilman, Magrath and Brinckerhoff,[7] in a preliminary communication, published a most notable contribution to the etiology of variola and vaccinia.

For variola they describe a double cycle, one cytoplasmic and the other intranuclear. The cytoplasmic stage commences with the presence, in lower layer of the epithelial cells of the skin, of small structureless bodies from one to four microns in diameter lying in vacuoles. These bodies increase in size, and develop a reticulated structure containing granules. These bodies undergo segmentation, leading to the formation of small round bodies about one micron in diameter. Their second or intranuclear stage begins with the invasion of the nuclei of epithelial cells by small round ring-like bodies, which occurs "at the period of segmentation, when most of the intracellular bodies have disappeared." These small ring-like bodies "increase in size and acquire a definite structure consisting of a series of vacuoles around a large central vacuole. The rim of the central vacuole stains more distinctly than do the other parts of the body. One or more of these bodies may appear in a single nucleus. When several are present they are smaller, but have the same structure. The body becomes larger, the nuclear rim grows less distinct, finally disappears and the body lies in a completely degenerated cell, or this breaks down, setting free the body. With the growth and development of the intranuclear body the vacuolar structure becomes less evident and finally a structure is formed which contains numerous fine vacuoles. At this time small circular bodies begin to appear in it and groups of these are surrounded by a faint ring, which probably represents the remains of the body in which they are formed. The circular ring-like bodies have a central dot. They are one to one and one-half microns in diameter, and are seen with great difficulty." They "regard this intranuclear body as a further stage of development of the intracellular body and as representing a second complete cycle of development. It develops from the spore-like bodies produced by segmentation of the intracellular body which

pass into the nucleus. They regard the bodies formed by its segmentation as the true infecting material of variola. They also give the results of their coworker Tyzzer, who studied vaccinia, in the lesions of which he found the intracellular but not the intranuclear cycle. Both cycles occur in inoculation variola in the monkey." Councilman and his coworkers described in this communication two definite and more or less complete cycles of development for the organism of variola and were able to point out clearly the reasons for the differences between variola and vaccina. This work was undoubtedly the greatest contribution to our knowledge of variola and vaccina since Jenner's discovery of vaccination.

In May, 1903, before the American Association of Pathologists and Bacteriologists, Councilman gave a detailed description of his work and illustrated it with lantern slides. Previous to the publication of his findings Councilman had written one of us (Dr. Howard) a description of his organism and the staining methods he used. As a result Dr. Howard was able to state at this meeting that by using these staining methods on his Cleveland smallpox material he was able in large part to confirm the observations made by Councilman and his coworkers.

Perkins and Pay, in 1903, gave the results of their study of the contents of vesicle contents in variola. They concluded that the bodies described by Dombrowski, Ishagami and by Funk in vesicle contents were not organisms, but various forms of cell degeneration. This work we regard as in a negative way confirmatory of Councilman's, for he does not find the organisms described by him free in the vesicle contents in recognizable form. In their second paper, Councilman, Magrath and Brinckerhoff,[3] after discussing the anatomy and histology of variola, review the literature with reference to protozoa and the cell inclusions of variola and vaccinia. They do not go into detail concerning their own findings, but give four plates, with thirty-four photomicrographs, illustrating the different stages in the cytoplasmic and intranuclear cycles described in their former article. One of their photographs also shows the intranuclear pansporoblasts more fully described by Calkins.

In the same number of the *Journal of Medical Research* containing this communication, Calkins[9] contributes an elaborate article, in which among other things, basing his study upon material and sections supplied him by Councilman, he gives an exhaustive description and interpretation of the organism described by Councilman, Magrath and Brinckerhoff.

Calkins makes out a much more complicated life cycle than that described by the latter observers. The following summary of his work is necessary in order that our own work may be understood and compared with his and with Councilman's:

1. AN EARLY CYTOPLASMIC STAGE. This agrees in the main with that first described by Councilman, Magrath and Brinckerhoff for human variola, but is more detailed. The smallest form (seven-tenths of a micron in diameter) is a minute homogeneous sphere which is all nucleus. One of the first indications of differentiation is central vacuolization with the occasional appearance of a minute central dot, which stains with methylene blue. Differentiation in the peripheral portion is first shown by minute unstained spots, which, with growth, increase in size and stain green in Borrel preparations, while comparatively large masses stain red. This red material forms the substance of the later developing gemmules and is called protogonoplasm by Calkins. Even at this stage there are evidences of ameboid activity. The organism is finely granular, without vacuoles or differentiation into ectoplasm or endoplasm. It may reach ten or fourteen microns in size. In the large forms the red staining protogonoplasm is usually in some stage of gemmule formation. When the organism is practically mature the granules of protogonoplasm lie each in a minute vesicle. These granules stain with most nuclear stains. These bodies are the gemmules, which are of the size and appearance of the smallest germs invading the cytoplasm. They escape by the disintegration of the framework, which remains as a residual structure in the cell host.

2. THE EARLY INTRANUCLEAR PHASE. (*a*) *Gametocytes.* The gemmules above described may develop into new cytoplasmic organisms (autoinfection) or ultimately may become germ cells within the nucleus. In the latter case they develop into structures re-

garded by Calkins as gametocytes, the products of which probably conjugate. The resulting zygote is the ameboid pansporoblast mother organism. Calkins bases this hypothesis upon the following observations: 1. In areas of the skin showing both beginning stages of invasion and reproduction of the cytoplasmic stage; early cytoplasmic forms are also found in nuclei. These go on to gemmule formation, the gemmules being fewer in number than in the cytoplasmic phase. He thinks these gemmules are connected with a sexual cycle, the mother organism being a female gametocyte. 2. The presence of groups of spheric bodies like the early intranuclear forms in the cytoplasm and the presence of ring forms among groups of gemmules remaining in the region occupied by the mother organism. These he regards as sexually mature gemmules which have failed to reach nuclei. Those reaching nuclei early assume a spheric form with central cell-staining masses, while later similar masses develop at the periphery. These are regarded as male reproductive elements. A fertilization stage is not made out.

(*b*) *The Zygote.* In many cases he finds definite intranuclear ameboid bodies with a deeply staining central mass of protoplasm which resemble the fertilized gametocyte of coccidium. Similar bodies are found in the cytoplasm. This intranuclear zygote-like body becomes the pansporoblast and the mother cell of the primary sporoblasts.

(*c*) *The Pansporoblast.* In the above-described intranuclear form the central mass of protogonoplasm fragments and is distributed throughout the substance of the organism. With growth the body reaches ten to twelve microns in size. Eight to twenty primary sporoblasts develop in it, leaving a large part undeveloped. This persists as a rest-body. The young sporoblasts are solid and homogeneous at first, but later become hollow and appear as thickened rings. On reaching from one to two microns in diameter the thickened periphery becomes vacuolated. Calkins describes two types of primary sporoblasts; in one the spores develop in peripheral vesicles and in the other in all the substance of the sporoblast. The method of spore formation is the same in both, namely, the accumulation of the spore-forming material about the

minute vesicles, forming darker spheres lining the spaces; these later segregate at one pole of each vesicle, forming a deeply staining body, with a characteristic vacuole. Each vesicle contains a single spore. These spores invade fresh nuclei, giving rise to secondary intranuclear phases.

3. SECONDARY NUCLEAR PHASES. The intranuclear spore thus formed, and resembling a vesicle thickened at one side, grows, and the thickened region ultimately extends around the vesicle. Minute vacuoles develop throughout the entire periphery. Secondary vacuoles then develop and the entire sporoblast (secondary sporoblast) becomes a mass of vesicles containing spores. With the escape of spores a sporoblast residuum remains.

It will be seen from the foregoing that the cytoplasmic and the intranuclear stages of Councilman, Magrath and Brinckerhoff correspond to the cytoplasmic and secondary nuclear stages of Calkins, and that Calkins' work has added materially to the complexity of the life cycle of the parasite. He adds an intranuclear stage due to the invasion of nuclei by gemmules, leading to the formation of bodies which he regards as male gametocytes, infers a conjugation between male and female gametocytes, describes a zygote form which forms an intranuclear pansporoblast, in which two forms of sporoblast develop, each producing spores which may invade fresh nuclei, there giving rise to secondary sporoblasts in which spores develop.

Magrath and Brinckerhoff,[10] in their studies upon the occurrence of cytorrhyctes variolæ in the skin of the monkey inoculated with variola, met with the cytoplasmic form, with both the last two series of intranuclear forms of Calkins ending in spore formation. They do not mention observing the invasion of nuclei by gemmules leading to the formation of male gametocytes.

III. STUDY OF OUR MATERIAL.

(*a*) *Source of Material.*

We had just begun to study sections of the skin in variola when we received news of his discovery from Dr. Councilman, and in a short time were able to confirm many of his observations.

Our material was derived from forty-nine autopsies on cases of variola dead at the Cleveland Smallpox Hospital and from skin excised from eight cases of variola in various stages of the disease. In one case skin was obtained in the early stages of the disease by excision during life and in later stages at autopsy.

Most of those dying of smallpox in the Cleveland epidemic died late in the disease during the late pustular stage and the period of desquamation. There were only nine autopsies furnishing skin suitable for study of the bodies described by Councilman and his coworkers.

Our autopises were made, as a rule, within an hour or two after death and portions of skin and other organs were fixed at once in Zenker's fluid. It may be stated that, as a rule, the autopsy material was as satisfactory for study as that excised during life.

Our work, therefore, is based upon the study of material from seventeen cases of variola.

(*b*) *Technic.*

All our material was cut in paraffin, the sections being from one to eight microns in thickness. Experience shows that sections from three to four microns thick give the most satisfactory results.

Staining Methods. 1. Mallory's iron hematoxylin, followed by aurantia, as used by Councilman.

2. Eosin and methylene blue as used by Malloy.
3. Eosin and methylene blue (Wright's mixture).
4. Aqueous fuchsin.
5. The Borrel method as advised by Calkins.
6. Magenta followed by methylene blue.

In our experience these stains have certain definite values in the study of the smallpox bodies. All stages may be studied by the Borrel and the iron hematoxylin and aurantia methods, the former being, as a rule, more generally satisfactory, because it gives finer details; however, most of the forms found with the former may also be discerned in sections staining by the latter method. Eosin and methylene blue are particularly valuable for the study of the early cytoplasmic forms, but are not satisfactory for the intranuclear stages.

Fuchsin does not give any details which may not be got by magenta or other stains.

Magenta followed by methylene blue has proved in our hands a very valuable stain for the early cytoplasmic stage; of the two stains the magenta has the stronger affinity for the protozoa, and the blue a stronger affinity for the nuclear chromatin. Sections are stained twenty minutes in aqueous magenta, washed in water, stained five minutes in methylene blue in potassium carbonate solution, as used by Mallory, differentiated in weak, followed by 95 per cent. and absolute alcohol and cleared in xylol. If differentiation is done with care the cytoplasmic bodies are stained pink or red and the nuclear rims and chromatin dots are stained deep blue, making a very strong contrast. The magenta is especially good, also, for bringing out the reticular meshwork of the cytoplasmic forms. The methylene blue and eosin combination as recommended by Mallory is very useful for the demonstration of the chromatin-like dots in the early growing cytoplasmic stage.

(c) *Description of the Stages of the Life Cycle of Cytorrhyctes Variolæ Observed by Us.*

1. PRIMARY CYTOPLASMIC STAGES. This stage is found in the early lesions and at the advancing margins of older lesions—progressive local autoinfection in which the stage is repeated by the invasion of the neighboring cells by the end forms (gemmules) of the stage.

This stage is best studied in the papule and early vesicle. The deeper layer of the epidermis is invaded by large numbers of small round homogeneous, deeply staining bodies which are found both in the cytoplasm of and between the epithelial cells. The smallest bodies are one micron or less in diameter and may lie in any portion of the cytoplasm without the presence of a vacuole. Somewhat larger forms hug the nucleus and lie in the perinuclear space, which is their favorite seat. As these bodies increase in size a comparatively large vacuole develops about each. The vacuole is usually round or long oval in outline. There is no membrane about the body or the containing vacuole. These bodies are intensely chromatophilic and stain with most of the nuclear dyes—

i. e., gentian violet, methylene blue, fuchsin, magenta, iron hematoxylin, etc., as well as with acid fuchsin and with eosin. In the presence of a nuclear and acid dye they select the former. They, unlike the chromatin of nuclei, have a stronger affinity for magenta than for methylene blue when these two stains are used in combination. At this stage there is no differentiation and the bodies stain homogeneously throughout. Forms considerably larger than these are round, oval, reniform, crescentic and occasionally dumb-bell in shape and still stain homogeneously with nuclear dyes.

Bodies attaining two or three microns in diameter are often irregular in shape and show differentiation with various staining methods. Stained with methylene blue and eosin (by Mallory's or by Wright's methods) the main mass stains deeply with eosin, while in the center there are one or many fine deeply stained blue points, suggesting masses of chromatin. By the Borrel stain the larger part of the bodies stain red, but there are larger and smaller unstained areas usually about the periphery and sometimes in the center.

Still larger and older forms show more marked evidences of differentiation, with definite change in structure. They are no longer homogeneous and refrangible, but are composed of a fine reticulum which stains with eosin, aurantia or magenta. The spaces of the reticulum are apparently empty. This reticulum closely resembles that of the bodies described by Mallory in scarlatina.

After this the bodies rapidly grow larger and very irregular in shape. Many are irregularly triangular and from some fine tapering pseudopodia-like processes project. Such forms vary from four to eight to ten microns in their largest diameter. They show marked and characteristic staining reaction with the Borrel stain, being marked by larger and smaller bars and dots and irregular areas of red upon a green background. All of the forms illustrated by Calkins' figures (1, 2, 4, 5, 6 and 7, Plate XVI.) were readily found in numerous sections from several cases, in material excised during life, as well as that obtained at autopsy.

In older lesions much larger cytoplasmic bodies, from six to sixteen microns in diameter, are found. These may be round,

oblong or long oval and have the appearance of ameba. Some are very long, and show a central tapering constriction. With Borrel's stain these forms stain pale green and may or may not show certain small red staining dots, varying in size from scarcely visible points to dots one-half micron in diameter. These dots stain homogeneously and deeply, are uniformly equidistant and are often arranged with mathematical precision. Round forms, apparently cut transversely, have the appearance of the top of a pepper-box (see Fig. 7). These larger forms almost completely fill the vacuole, cause enlargement of the cell and displace the nucleus.

Occasionally in Borrel sections ameba-like bodies, apparently cut transversely, are found which show a definite but fine meshwork or alveolar structure. The alveolar spaces may be apparently empty or may contain granular material, staining green. The meshwork may stain green or red, but always shows minute nodular refrangible thickenings which stain bright red. These red points are sometimes found in the length of the strands of the meshwork or alveolar framework, but are more numerous at the junction of several strands—*i. e.*, at the corners of the alveolar spaces. These bodies lie in definite vacuoles, which they may fill, and the cells containing them show well-staining nuclei.

The large ameba-like forms above described develop a number of deeply staining, solid, homogeneous bodies of the size and appearance of the earliest forms seen in the papular lesion.

These bodies stain well with methylene blue, iron hematoxylin, magenta or fuchsin. They lie in the spaces of a meshwork from which they escape into the cytoplasm of the cell containing the body from which they developed and finally make their way into the intercellular spaces. The meshwork is left as a residual mass which stains with iron hematoxylin and with the magenta of the Borrel mixture.

This stage of the cycle of the parasite ends with the formation of the gemmule of Calkins, a body similar in size, shape and staining reactions to the primary invading form of the papular stage. The completion of this stage corresponds with the beginning vesicle.

We have never observed the development of this stage of the organism in the nucleus at any stage of the disease.

Some of the gemmules invade the cytoplasm of neighboring cells, especially in the deeper layer, at the margins of the vesicle. As in the primary invasion, they show a greater affinity for the epithelial cells of the deeper layers. The variola process extends laterally by this secondary invasion, where the organisms repeat the developmental stage above described.

We have been unable to make out conjugation of gemmules with each other or with other structures in the lesion.

Judging by the next stage of the cycle, it is not improbable that conjugation in some form does occur at this time.

We have occasionally seen in early lesions gemmules with a single long wavy cilium. Such gemmules usually lie in vacuoles in cells, the cilium projecting through the cell into the surrounding intercellular spaces. These were seen only in sections of excised skin.

2. Secondary Cytoplasmic Stage. This stage is not described by previous observers, but Calkins has certainly seen a small portion of it. On pages 151 and 152 of his article, in describing the zygote, he states: "Certain definite bodies are frequently found in many different cases which resemble the fertilized female gametocyte of coccidium. These are more or less ameboid forms within the nucleus, characterized by a deeply staining body and a central nucleus-like mass of protogonoplasm. *Occasionally a similar ameboid organism is found in the cytoplasm, one which I observed being surrounded by a very definite capsule and clearly differentiated into the cytoplasm and nuclear mass, while the remainder of the cell in which it lay had no trace of parasites.*"

We have been able to trace the development of these bodies in the cytoplasm in four cases. While the beginning of this stage is still shrouded in obscurity we have observed the greater portion of it as follows:

In fairly well-developed vesicular lesions, after complete gemmulation of most of the organisms of the primary cytoplasmic stage, in the cytoplasm of the deeper layer of epithelial cell numerous definite bodies are seen in various stages of development. The earliest forms which we have definitely traced are from two to

three microns in diameter, round or oval in outline, and are surrounded by a definite membrane (spore membrane ?). These bodies lie in the cytoplasm, usually some distance from the nucleus, and are not surrounded by a vacuole. Cells containing these forms have normal nuclei. The bodies stain with various dyes. In the smallest no chromophile material is found, but larger forms contain from one to four round dots which stain deeply with nuclear dyes. With the iron hematoxylin and aurantia stain the main mass stains with aurantia and the chromatin-like dots and the membrane stain with hematoxylin. The main mass is homogeneous and structureless in the younger forms. In somewhat larger forms with four chromatin-like dots, which are situated so that each dot lies in a separate quadrant of the circular body, the cytoplasmic mass becomes separated into four portions by faint lines of cleavage, suggesting segmentation or fragmentation. These lines are definite and distinct; they can best be made out by the use of the Ziess oil-immersion lens and the 12 eye-piece. In the larger forms fragmentation or segmentation is readily seen; the round or oval body is cut up by definite lines into four (or more) oval bodies with hyaline or finely granular cytoplasm which stains yellow with aurantia, and each contains a small dot staining deeply with iron hematoxylin and situated near the center. At this stage these bodies are closely crowded together and are still surrounded by a thin membrane. In some areas most of the epithelial cells contain these definite structures. In the further development of this stage some epithelial cells contain from four to eight such bodies, lying usually in a clear space in the cytoplasm. The membrane disappears. After the escape of the bodies from the membrane they enlarge, become finely granular and usually retain their oval shape. Some cells contain at least eight such bodies, which distend the cytoplasm and cause enlargement of the cell. The nucleus is pushed to one end and is shrunken and shrivelled. No residual mass is discernible.

At this stage and later large numbers of these small oval or circular bodies are present singly and in groups in the intercellular spaces. In cells in the immediate neighborhood a single identical body is found in the cytoplasm of some and in the nucleus of others.

After the escape of these bodies from the cells in which they develop they increase in size and some become round. The cytoplasm of the bodies becomes finely granular, stains green with the Borrel mixture, while the nucleus-like mass of chromatin stains red. Not all of these bodies invade nuclei and there is evidence that some may grow and develop in the intercellular spaces, for occasionally large forms are found here closely resembling those to be described below as occurring in the nucleus.

While we have not been able to trace the earliest forms of this secondary cytoplasmic stage, in a number of sections we have observed certain bodies situated in the cytoplasm of the deeper epithelial cells. These bodies are from one-half to two microns in diameter and are surrounded by a thin membrane, which, like the body itself, stains green with Borrel's stain; no red staining areas are seen. The body takes the form of a thick ring or concave disk. Preceding the appearance of the earliest forms of this secondary cytoplasmic stage no evidences of conjugation or other change of the gemmules leading to their formation are seen.

3. Primary Intranuclear Stage. This is never seen before the secondary cytoplasmic stage has been completed for some organisms at least and does not follow immediately upon the completion of the primary cytoplasmic stage. The primary intranuclear stage begins with the invasion of epithelial cell nuclei by the oval or round bodies set free from the completion of the secondary cytoplasmic stage. Calkins, as before remarked, has traced this stage through to the development of primary sporoblasts forming spores, starting from a solid intranuclear form X of unknown origin, but which corresponds exactly to the bodies we describe above.

The earliest primary intranuclear forms may be either oval or round, more often the latter. They are composed of a finely granular cytoplasmic mass with a central deeply staining nucleus-like body. The latter stains with methylene blue, fuchsin, iron hematoxylin and the magenta of the Borrel mixture. The cytoplasmic mass stains green with Borrel and yellow with aurantia. The body does not fill the nucleus, the chromatin of which is pushed aside. Otherwise the nucleus in the early stages appears normal.

These intranuclear bodies vary from three to eight microns in diameter. Rarely two occupy a single nucleus. No evidence of conjugation is distinguished. As the bodies increase in size a number of small dots, which stain deeply with nuclear dyes, develop in the granular cytoplasm. There is no apparent diffusion of the nucleus-like body, which also increases in size. At this time these bodies closely resemble the large primary cytoplasmic forms, from which, however, they are readily distinguished by their intranuclear position and the prominence of the central nucleus-like body, which is absent in the primary cytoplasmic stage.

In bodies somewhat larger, which are more often oval than round, there are among the numerous deeply staining solid dots in the organism a larger or smaller number of ring-shaped bodies with clear contents. The rings are, as a rule, larger than the deeply staining dots. Later all the dots give place to ring bodies which correspond to the primary sporoblasts of Calkins. At this stage the main mass of the organism, or the pansporoblast of Calkins, still stains green with Borrel, while the dots and rings (sporoblasts) stain red. The latter stain well, also, with iron hematoxylin, while the pansporoblast stains with aurantia. From this point there are two modes of development. In the first, which is in our experience the least common, the vesicles or rings in the pansporoblast enlarge, remain hollow in the center, and form peripheral vesicles, each containing a small deeply staining dot which represents the spore (see Calkins, Figs. 51 and 54, Plate XVIII.). In the second the rings or sporoblasts are very numerous and develop throughout the substance of the organism. The rings are crowded together in such a mannner that their margins are in close apposition and the body has a distinct morula appearance (see Calkins, Figs. 67, 68 and 69, Plate XIX.). The rings or sporoblasts contain small deeply staining dots.

Calkins recognizes these two types of primary sporoblasts (see page 154) and thinks that the "difference is due to imperfect fixation, or merely an optical effect due to flattening of the usually spheric body." The deeply staining dots represent the spores. On close examination the spores are found to be composed of a vesicle or vacuole, thickened at one side. They stain red with

Borrel and black with iron hematoxylin. They may occasionally be found in numbers in the surrounding tissue. We have been able to trace the whole stage as given by Calkins. In our sections pictures identical with his Figs. 33 to 48, Plate XVIII., are common, and that all these forms occur in sequence is beyond question of doubt.

Forms like his Figs. 67, 68 and 69, Plate XIX., representing our morula forms, we find frequently.

In the first method of sporoblast formation a large part of the pansporoblast is often left as a residuum. With the growth of the pansporoblast the nuclear rim may be broken and the organism escape before the spores are fully developed.

4. Secondary Intranuclear Stage. The beginning of this stage is marked by the appearance in epithelial cell nuclei of small ring-shaped bodies identical in structure, appearance and staining reactions with the bodies set free on the completion of the primary intranuclear stage. From one to five or six such forms may be found in a single nucleus. They invade the nuclei of cells, usually of the deepest layer, in the neighborhood of the nuclei affected in the primary intranuclear stage.

The first evidence of development shown by the secondary intranuclear bodies or spores is increase in size, accompanied by increased thickness of one side of the rim, with the formation of one or more small vacuoles at this point. The body, then, is composed of a central vacuole or vesicle, surrounded by a rim, from which in turn there spring a larger or smaller number of small secondary vacuoles or chambers with thin walls. Finally the whole original enlarged ring body is surrounded by a single or by multiple rows of secondary chambers with thin walls. These vacuoles or chambers are apparently empty and their walls of uniform thickness. A somewhat dense but vacuolated body is sometime seen within the large vacuole. Later small points staining deeply with the magenta of the Borrel stain, or with iron hematoxylin, appear in the chambers. These chromophile dots lie in a clear material which surrounds them like a halo. These bodies are set free by the disintegration of the intranuclear form and correspond in all respects to the spores of Councilman and Calkins.

Throughout its development the secondary intranuclear stage stains deeply red with magenta and fuchsin and black with iron hematoxylin. In old lesions the empty residual bodies left on the escape of the spores may be found staining green with the Borrel stain as described by Calkins. Not infrequently, as also pictured by Calkins, the secondary intranuclear forms produce a single set of chambers about the original ring body.

Several of the secondary intracellular forms may develop in the same nucleus, in which case they are small, but in other respects identical with the larger single intranuclear bodies.

(*d*) *Summary of the Stages of Cytorrhyctes Variolæ as Described by Us.*

1. PRIMARY CYTOPLASMIC STAGE FOUND IN THE EARLIEST LESIONS AND IN AUTOINFECTION ABOUT VESICLES. This stage begins with a small, round, homogeneous deeply staining body which develops into a large ameboid multichambered organism and breaks up with the discharge of gemmules identical with the bodies primarily invading the epithelial cells.

2. SECONDARY CYTOPLASMIC STAGE. The earliest forms recognized are from one and one-half to two microns in diameter, surrounded by a definite spore or egg(?) membrane. These grow, develop chromophile dots, fragment or segment, with the formation of oval cytoplasmic bodies with a central chromatin mass. From four to eight of these oval segmented bodies may be present in a single cell. These bodies escape from the cells in which they develop, invade other cells and reach their nuclei, where they further develop, being the earliest stage of the

3. PRIMARY INTRANUCLEAR STAGE. These ameboid bodies, representing the pansporoblast, first develop numerous dense dots staining deeply with nuclear stains. These dots later become rings —the primary sporoblasts in which spores develop.

4. SECONDARY INTRANUCLEAR STAGE. This stage begins with the invasion of fresh nuclei by the spores of the preceding stage, which form secondary sporoblasts developing numerous chambers, each containing a spore.

(e) *Comparison of the Results of Our Studies with those of Councilman, Calkins and their Coworkers.*

1. We confirm their primary cytoplasmic stage *in toto*, having been able to follow every step and to find every form of it as described by them.

2. While not in any way wishing to deny the occurrence of the invasion of nuclei by gemmules, with the resulting formation of male gametocytes, as described by Calkins, we have not, after careful search of our material, been able to confirm his observations on this point. We have not been able to satisfy ourselves that the gemmules ever invade nuclei. However, further study of additional material may change our opinion on this point.

3. We have been able to trace a large portion of a secondary cytoplasmic stage, beginning possibly with conjugation and ending with the formation of round or oval bodies, the products of a definite segmentation or fragmentation. These bodies invade nuclei and are the earliest forms of the primary intranuclear stage of Calkins.

4. Our work confirms the whole of the primary intranuclear stage of Calkins without modification.

5. We also confirm all of the secondary intranuclear stage of Calkins. This is evidently the intranuclear stage first described by Councilman, Magrath and Brinckerhoff, to whose description little has been added.

IV. RELATIONS OF THE PARASITE TO THE SKIN LESIONS.

Corium. The earliest lesions occur here, before the epithelium shows any change. This is best studied in skin excised from early cases. The vessels of the papillæ in the affected areas show marked changes. The blood capillaries are dilated and in the non-hemorrhagic cases contain few erythrocytes and leukocytes. The endothelial cells are swollen, often desquamated and in some cases increased in number. Definite breaks in the walls of the vessels are often seen. There is commonly proliferation of the endothelial cells lining the perivascular lymph spaces. In and about these mononuclear leukocytes not infrequently accumulate. Occasionally small homogeneous,

deeply staining bodies, in every way identical with gemmules, may be seen in the blood and lymph vessels and between them and the membrana propria of the skin. In early hemorrhagic cases these changes are also present, but the bloodvessels are distended with blood (in which the leukocytes bear about the normal proportion to the erythrocytes), with larger and smaller areas of hemorrhage. The hemorrhage is due both to diapedesis and to actual rupture of the capillary walls. We were not able to make out definite endothelialysis, but in some vessels thrombosis due to agglutination of erythrocytes was observed. The hemorrhage and congestion in hemorrhagic cases often obscures the vascular changes. Similar vascular changes are often found deep in the corium. We have devoted a great deal of study to the endothelium of the papillary vessels, looking for evidences of a possible cytoplasmic or nuclear stage of the parasite in these cells. This study was, however, entirely negative. Gemmules may undoubtedly, as Councilman, Magrath and Brinckerhoff first showed, be present in the bloodvessels, but evidence of the occurrence of a cycle in these cells is lacking. The gemmule is the only form of the parasite found by us in the vessels and tissues of the corium.

In the late vesicular and pustular stages of the disease extensive changes often occur in the papillæ. They comprise edema, hemorrhage, leukocytic invasion and even necrosis.

Epidermis: The gemmules reach the epidermis from the papillary vessels; some invade the basement or deepest layer of cells, but others make their way through the intercellular spaces and invade cells, three, four or even more rows above the membrana propria. In a well-established lesion the oldest forms are not usually found in the deepest cells. It is evident that not all of the invading organisms reach the epidermis at the same time. The changes in the papillæ above described and the invasion of the epidermis mark the papular stage of the disease. In most cases at this stage the majority of the cells do not harbor organisms.

The gemmules may be found in any portion of the cytoplasm, but most finally make their way to the perinuclear space. At first they lie embedded in the cytoplasm without vacuolization of the latter. As they increase in size vacuoles always appear about

them. We have never at this stage seen any other form of cell inclusion but the gemmule.

The earliest change in the invaded epithelial cells is the formation of a vacuole about each parasite, one or three or four of which may invade a cell. As the organism grows the invaded cell increases in size, reaching, finally, several times the size of uninfected cells. The organism may reach considerable size without producing marked changes in the nucleus. The latter is, with the growth of the parasite, displaced, the nuclear membrane may become swollen, irregular or shrunken and the nucleus, with the disintegration of the cell, finally disappears. The nucleus never undergoes any form of degeneration simulating the intranuclear phases of the parasite. The cell may or may not disintegrate with the completion of the primary cytoplasmic stage. The residual mass of the latter is commonly found in the cell. As the organism of the primary cytoplasmic stage grows, fluid accumulates in the lesion, derived partly from the papillary vessels and partly from the breaking down of epithelial cells. Few leukocytes and erythrocytes (except in hemorrhagic cases) are found in the earlier lesions. The fluid tends to make its way to the upper layers of the epidermis, which finally become elevated and separated from the lower layers. The invading leukocytes also tend to accumulate here rather than among the deeper cells. The parasites, on the other hand, are found most abundantly in the deeper portion of the epidermis. The secondary cytoplasmic stage always occurs in the deeper cells, usually in those of the first three or four rows. This phase always follows the primary cytoplasmic. In small lesions an apparent gap in the cycle is usually present; that is, the primary cytoplasmic phase is complete and no intranuclear forms are seen. This is the time to find the stages of the secondary cytoplasmic phase. In most such lesions these forms are few in number, while in others, notably in sections from Cases 37 and 39, they are found in great numbers.

The beginning of the primary intranuclear stage is definitely associated with the completion of the secondary cytoplasmic. These stages frequently overlap in the sense that the secondary cytoplasmic stage is complete in some cells and progressive in others,

while the invasion of the nuclei of other cells by the products of this stage has begun. In some sections the deeper part of the lesion is flooded with segmented secondary cytoplasmic forms. Not all these forms reach nuclei, some are apparently capable of a certain amount of development outside of nuclei, for half-grown pansporoblasts may be found in the intercellular spaces. We have no evidence, however, that this stage may be completed in this situation. As pointed out by Calkins and confirmed by us, the developing pansporoblast may break through the nucleus and escape from the cell, and it is impossible to discriminate between those which have and those which have not invaded nuclei.

On the completion of the primary intranuclear stage large numbers of spores may sometimes be seen free between the cells.

The secondary intranuclear phase is also largely confined to the deeper rows of epithelial cells. During this stage in many lesions few of the remaining cells in this part of the lesion are free from intranuclear parasites. The spores of the secondary intranuclear stage are much less readily found free than those of the primary intranuclear stage. This is in some measure due to the greater amount of cytoplasmic and nuclear detritus present at this time. We have never recognized the parasites in any stage in leukocytes. During and at the end of the secondary intranuclear stage often large numbers of leukocytes, many degenerated and with marked nuclear fragmentation, are found in the epidermis and in the papillæ in the region of the lesion.

The completion of this stage marks the end of the progress of the lesion, but about the margins of such lesions autoinfection with the primary cytoplasmic form is sometimes seen. Whether these reach maturity or not it is not possible to state.

We have not distinguished any stages of the parasite in the healing pock.

The work of Councilman, Magrath and Brinckerhoff on variola, and of Tyzer on vaccinia, has so conclusively shown the relation of these bodies to the lesions of these diseases, and Calkins has so clearly established their position as protozoan parasites, that it seems unnecessary to us to restate the arguments which they have brought forward to prove that the above-described forms are living

organisms and the cause of the disease. That they are neither artefacts nor the products of cell degeneration, we think Councilman[11] has conclusively shown in his epicrisis.

V. CONCLUSIONS.

1. The bodies described in the skin lesions of variola by Councilman and his coworkers represent stages in the life cycle of a protozoan parasite.

2. We have been able to confirm all of the cycle as made out by Calkins, except the invasion of nuclei by gemmules, these going through a stage leading to the formation of male gametocytes.

3. Based on the study of our material we can rcognize a primary and a secondary cytoplasmic and a primary and a secondary intranuclear stage. The end forms of these stages are: (*a*) the gemmule; (*b*) large solid nucleated forms—the zygote-like body of Calkins; (*c*) small ring-like spores in both the intranuclear stages.

4. The relation of these parasites to the skin lesions is of such a definite and intimate character as to lead to the conclusion that they are the cause of the disease.

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ON THE ETIOLOGY OF BACILLARY DYSENTERY AND OF CATARRHAL ENTERITIS IN CHILDREN.

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DESPITE the marked activity of the last few years in studying the bacteriology of dysentery, it cannot be said that we have yet obtained a wholly clear idea as to the condition and its causation. Only very recently have we obtained evidence showing that confusion is largely due to the attempt to ascribe a common etiological factor to all cases. But even now, with our knowledge that there is more than one form of colitis with bloody stools, there is still need of further study of the symptoms and morbid anatomy of the different forms in order to differentiate them properly. It is possible, also, that we may fail to recognize that this colitis may be due or may, at least, owe its symptoms to various combinations of groups of microbes, allied or unrelated. It was with the object of studying more carefully the bacteriology and symptomatology of cases presenting themselves in a children's hospital with dysenteric symptoms that the present study was undertaken.

ON THE TYPES OF DYSENTERY. As already indicated, much confusion of terms has arisen by attempts to classify the various cases at a time when the etiologic factors were not perfectly known. Thus Osler has described four varieties: the acute, catarrhal, diphtheritic and the tropical or amœbic dysentery. Kartulis describes

endemic, epidemic and sporadic varieties. Manson speaks of a catarrhal and an ulcerating dysentery. Since we have known more regarding etiology, Kruse[1] has recognized four different types:

1. That caused by infection with the Shiga bacillus, and so termed by him *Dysenteria japonica.*

2. That due to infection with the Kruse strain of dysentery bacillus, hence called *Dysenteria germanica.* Already we know that these two may be regarded as one, for the Shiga and Kruse strains are identical.

3. *Institutional dysentery* or *pseudodysentery,* caused by a bacillus isolated by Kruse from the stools of dysenteric patients in an epidemic in an insane asylum, and distinguished from true dysentery not only in the different cultural characters of the organism isolated, but also by the fact that the blood of those affected failed to agglutinate a culture of the true dysentery bacillus. This pseudodysentery bacillus we may here note is identical with that isolated by Flexner two years previously at Manila, concerning which we have more to say in the following pages.

4. *Amœbic Dysentery.* Regarding this last, Leonard Rogers[2] has pointed out that amœbic dysentery is separated from bacillary dysentery by certain well-marked differences. In the uncomplicated cases the dysentery bacillus is not present in the stools, the serum of those affected does not agglutinate any of the strains of the dysentery bacillus, and the pathologic lesions found in the intestines possess certain characters not seen in cases of bacillary dysentery. It will be seen thus that the *commoner* forms of endemic and epidemic dysentery become reduced to three: dysentery proper, with which is associated the Shiga bacillus; institutional dysentery or pseudodysentery, in connection with which the Kruse or, more correctly, the Flexner bacillus is found; and amœbic dysentery.

Previous observers, notably Booker,[3] Maggiora,[4] Arnaud,[5] Celli and Fiocca,[6] had failed to find any of these organisms. It may be that they had, in the absence of finer means of differentiation, confused them with cultures of the colon bacillus. But several of these observers and Blachstein[7] had shown that, either by employing virulent cultures of the B. coli or by exalting the virulence of

cultures of this organism by passage upon injection, they were able to produce in the lower animals a condition simulating dysentery in some particulars. Another organism, the bacillus pyocyaneus, may here be noted as having been found by Calmette[8] and by Lartigau[9] in association with epidemics of dysentery; while more recently Le Dantec[10] has described a dysentery associated with the abundant presence of a spirillum.

Shiga's bacillus was discovered by that observer in Japan, in connection with epidemics having a high mortality, in the years 1897–1898.[11] The bacillus was not found in the stools of the non-dysenteric patients or those of healthy individuals. Kruse,[12] Rosenthal[13] and others have isolated bacilli from the stools of dysenteric patients in Germany in all respects identical with that described by Shiga.

Flexner's bacillus was isolated from cases of epidemic dysentery in the Philippine Islands in 1900.[14] At first thought to be identical with that described by Shiga, the studies of Martini and Lentz,[15] confirmed more recently by those of Hiss and Russell,[16] have shown definite distinctions between the two forms; Flexner's Manila type ferments dextrose, saccharose, maltose, galactose, lævulose and mannite, with acid production; whereas the Shiga bacillus produces acid only in the presence of dextrose, galactose and lævulose; while it is found that cultures of the two types react differently toward immune sera prepared from the two varieties; an immune serum prepared from the Shiga bacillus will agglutinate a culture of the Flexner type in high dilutions; an immune serum prepared from the Flexner bacillus agglutinates cultures of the Shiga bacillus only in low dilutions.

Still more recently various epidemics of dysentery in America have been investigated by Wollstein,[17] Gay and Duval,[18] Park and Dunham[19] and others, and cultures of both the Shiga and Flexner types of bacillus have been isolated; the serum reactions of the blood of the different patients have been tested with cultures of both types of bacillus. The number of infections in which the Shiga bacillus has been found is small in comparison to the number in which the Flexner type has been obtained. The serum reactions have been variable and not always present, but, in

general, cultures of the Shiga bacillus appear to have been agglutinated, either not at all or else in low dilutions, by the serum of patients infected by the Flexner bacillus; while, on the other hand, the serum of those patients who have recovered from the infection of the Shiga bacillus have shown much greater agglutinative power not only toward the Shiga bacillus, but also toward cultures of the Flexner bacillus. This has also been the experience of Kruse in the epidemic of true dysentery studied by him and in an epidemic of pseudodysentery in which the bacillus isolated corresponded most closely with the Flexner Manila bacillus. The results which have been obtained by the study of dysentery in Vienna correspond with those of Martini and Lentz and the later workers both as regards cultural as well as agglutinative properties of these types or groups of bacillus.

Outline and Source of the Material Investigated. With the exception of three adult males who became infected with the bacillus dysenteriæ (Shiga), when working with either cultures or material derived from a group of cases of true dysentery, the material under investigation has been from children admitted to the wards of St. Ann's Kinderspital, ranging in age from one week to five or six years. The entire work has been carried out in duplicate by independent observers,* and many of the more important portions have been repeated by other workers in order to eliminate all possibility of error.

The cases studied may be divided into four groups, as follows:

1. The Shiga-Kruse or true dysentery group, including patients from whose fæces only the Shiga type of bacillus was isolated.

2. The Flexner or pseudodysentery group of patients, from whom only the acid-producing or Flexner type was obtained.

3. The enterocolitis or catarrhal diarrhœa group of patients, from whose fæces neither the Shiga nor the Flexner type of bacillus was isolated, the condition being due apparently to various organisms.

4. The control group, comprising non-dysenteric patients and normal individuals.

* Each step, that is, in the investigation made by one of us (G. A. Charlton) has been controlled and independently confirmed by the other (Ludwig Jehle), who also studied the cases of true dysentery in the adult which occurred at the hospital before the main investigation was started.

In addition to the cultures isolated from the stools of patients we have had for study and control original cultures of :

1. B. dysenteriæ (Shiga) ; (*a*) direct from Japan; (*b*) from Professor Paltauf, Director of the Austrian Bacteriologic Laboratory and Franz Joseph Serum Institute, Vienna. From the latter we obtained four strains, namely, " Paltauf," "Petronella," " D'Anna," and "Ghon." These cultures are from various sources and different epidemics throughout Austria and Germany, and, both culturally and as regards agglutinative properties, were confirmed by us as identical in every respect with the cultures of the Shiga bacillus received from Japan.

2. Cultures of Bacillus coli communis (Escherich) and of Bacillus typhosus (Eberth) were also supplied by the Bacteriologic Institute.

3. A culture of Flexner's Manila strain of dysentery bacillus. The Austrian Serum Institute also supplied us with immune horse sera prepared from (1) the Bacillus dysenteriæ (Shiga) ; (2) the Bacillus coli communis (Escherich); and (3) the Bacillus typhosus (Eberth), as also with normal horse serum.

The cultures of both types of dysentery bacillus, as well as allied forms, have been tested as regards their agglutinative reaction with all these immune sera as well as with the sera both from the hosts and from other patients.

TECHNIQUE. The stools were collected in suitable utensils previously sterilized by boiling, and were examined in as fresh a condition as possible, usually within a few minutes after they were passed. This immediate examination is important, for it is found that when kept for but a short time, especially in the case of dysenteric stools containing much blood, it becomes extremely difficult to isolate cultures of the bacillus dysenteriæ, the bacillus apparently being destroyed by the bactericidal activity of the blood, and leaving only bacillus coli and allied forms.

The general character of the stools having been noted, a fresh unstained portion as a representative sample was examined microscopically; a similar proportion stained by Gram's method was made and studied in order to ascertain the morphologic forms present; then, from a similar portion suspended in normal salt solution in a sterile Petri dish, a series of agar plates was inocu-

lated and incubated at 37° C. for twenty-four hours. As a rule, the stools from each case were examined daily during the acute period of the disease and afterward at intervals until the patient was discharged.

The agar medium used for plating was exactly neutral to litmus and was prepared from bouillon made from horse flesh. It was found that this gave much better results than that prepared from beef, and, in addition, it was much less expensive. When the stools from cases of enterocolitis were to be plated, 1 per cent. of glucose was added, as on the sugar plates more forms of bacteria appeared, especially forms staining by Gram.

At the beginning of our investigation we followed the technique described by Flexner, namely, that of transferring the colonies appearing on the agar plates into 1 per cent. glucose agar tubes as stab cultures, rejecting as bacillus coli all those cultures which produced gas. This method was abandoned, however, as being too restricted for our purpose, which was to ascertain as nearly as possible wherein the flora of the dejections of patients suffering from dysentery and the severe types of diarrhœa occurring in children differ from those of non-dysenteric patients and the micro-organisms of normal stools, rather than to search for any single organism or group of organisms. Instead, therefore, of the glucose agar stab cultures there was substituted the following fluid medium devised by Lentz[30] and composed of peptone (Witte), 10 grams; sodium chlorid, 5 grams; mannite (Merck's alcohol precipitated), 10 grams; 5 per cent. aqueous solution of litmus (Merck's highly pure), 10 c.cm. Distilled water 1000 c.cm.

This medium, easily prepared, does not undergo change during sterilization, is as free as possible from impurities, and, whether used anaërobically in the bent fermentation tube, or aërobically, always gave definite and satisfactory results. Except for the purpose of estimating accurately the amount of gas produced by the organism, our method of using this medium was most convenient, and it was economic of material and incubation space—important considerations when hundreds of cultures are to be studied. We used this medium in aërobic cultures in narrow test-tubes, 6 cm. long by 0.5 cm. in diameter; 1 c.cm. to 1.5 c.cm. of the medium was

sufficient for a culture. In these narrow tubes any gas, even slight traces, which may be produced adheres to the inner surface of the glass, and is readily detected. The only organisms so far met with occurring in fæces which are able to produce gas and acid in this mannite medium are bacilli of the colon group. Therefore, in rejecting the gas producers by means of mannite instead of glucose the Gaertner bacilli and the paracolons are retained. The Flexner bacillus, bacilli of the paracolon and paratyphoid groups, B. typhosus and Bacillus Y (Hiss) produce acid in presence of mannite, but no gas. The pyogenic cocci produce only sufficient acid to render the media purple. B. dysenteriæ (Shiga-Kruse) does not ferment mannite and therefore the medium remains blue and unchanged. Thus the various colonies appearing on the agar plate are, by one operation, divided into three groups and can then be studied at leisure. The morphology of the members of each group was determined by hanging-drop and stained preparations, and, for final differentiation and classification the method described by Hiss and Russell[21] was adopted; but, instead of fermented sugar free bouillon, which is unsatisfactory unless prepared with great care, 1 per cent. peptone-water was used, to which was added 1 per cent. of either of the following carbohydrates: dextrose, saccharose, lactose, mannite, maltose, galactose, inulin and dextrin—all chemically pure Merck preparations—and the media were colored blue by adding 1 per cent. of a 5 per cent. aqueous solution of Merck's pure litmus. It is preferable in making these media to first prepare the peptone-water and sterilize twice on successive days at 100° C., then add the proper amount of carbohydrate and litmus solution—the latter previously sterilized—and sterilize twice or thrice at 90° C., thus avoiding, as much as possible, the splitting of the carbohydrates by overheating.

When grown in these media it will be found that:

B. fæcalis alkaligenes does not ferment any of the carbohydrates, the media remaining blue and unchanged.

B. dysenteriæ (Shiga) ferments glucose and galactose only with acid production.

B. typhosus ferments glucose, mannite, maltose, galactose and dextrin, with production of acid.

The Flexner Manila bacillus ferments glucose, saccharose, mannite, maltose, galactose and dextrin, with production of acid, thus standing midway, as it were, between B. typhosus on the one hand and B. coli communis (Escherich) on the other, the latter fermenting glucose, lactose, mannite, maltose and galactose, with production of gas and acidity and producing acid without gas in dextrin broth.

By means of these tests, in addition to those commonly employed, the relationship, at least culturally, which exists between allied bacteria is distinctly brought out, and when the intestinal bacteria of the domestic animals, as well as man, have thus been studied many valuable data will have been acquired. The results obtained with some of the organisms at present under investigation indicate that, in general, differences in agglutination reactions of bacilli, at first thought to be identical, are due to the fact that, as shown under this method, they are in reality different, though closely allied organisms, whereas bacilli which are culturally identical under these tests differ but slightly in agglutination reaction when tested with the same immune serum.

Technique of Serum Reactions. The blood from which the dilutions of serum are prepared was obtained by piercing the lobe of the patient's ear, previously sterilized with alcohol and ether, when not more than 1 to 2 c.cm. were required ; larger quantities were obtained from the median basilic vein. Immediately after being obtained, the test-tubes containing the blood were placed in the incubator for twenty minutes at 37° C., then put on ice for an hour or more, and, if needed at once, the corpuscles were thrown down by centrifuging for five to ten minutes. The methods of making the dilutions and the technique regarding the observations of the reactions, both macroscopic and microscopic, were in every particular the same as those employed by Theobald Smith.[22]

General Character of the Cases Investigated. In all 60 cases have been studied ; 9 of these were cases of true dysentery, and from their dejecta only B. dysenteriæ (Shiga) and B. coli were isolated. In a second group of 13 cases of pseudodysentery, from whose stools the Flexner bacillus was isolated along with colon forms, the B. dysenteriæ (Shiga) was not found. The remaining

38 cases are those from whose stools neither the Shiga nor the Flexner bacillus was isolated, 28 cases being various forms of diarrhœa in children, while 10 were normal children not suffering from intestinal disturbances.

1. *Cases Yielding B. Dysenteriæ (Shiga).* Previous to the summer of 1903 true dysentery had been rarely met with in Vienna, although epidemics had appeared from time to time in several of the smaller cities and towns in Austria. During July and August, 1903, however, a number of cases of the disease occurred in Vienna, and 6 of these were admitted to the wards of St. Ann's Kinderspital. Later, 3 other cases occurred within the hospital, the infection being derived from the first cases. Four of these patients died, and that during the first few days of the disease, giving a mortality of 44.4 per cent. At the autopsy the lesions found in the intestines were similar to those described by Kruse. The stools of these patients numbered from 30 to 50 per diem and during the acute stage consisted almost entirely of blood. Later, as the disease passed into the subacute stage, the quantity of blood diminished, the stools being composed of softening portions of diphtheritic membrane, round or elliptical in shape, and varying from the size of a split pea to 1.5 cm. by 0.5 cm. in dimensions or larger. Of these, one surface was grayish, the other bloodstained, as though coming from an ulcerating surface. These portions of membrane were made up of epithelial cells, red and white blood corpuscles and numerous bacteria, the whole bound together by gelatinous mucus. The amount of this diphtheritic discharge gradually diminished and, after three or four weeks, the fæces resumed their normal appearance. During the acute and subacute stages the patients suffered constantly from extreme abdominal pain, with tenderness over the region of the colon. The tenesmus in the acute stages was very marked. There was little or no fever at any time.

The Shiga bacillus was present in the stools of these patients in almost pure culture during the acute stage, and colon forms were also present, but the Flexner bacillus could not be found. The Shiga bacillus was absent from the urine in all cases, though cocci and the bacillus coli were fairly abundant. At the autopsy the Shiga bacillus could not be cultivated from the blood and internal

organs, though it was present in the walls of the intestines and in some of the mesenteric glands; but the blood and internal organs gave the colon bacillus with, in some cases, cocci.

The cultures of Shiga bacillus isolated from the stools were all of high virulence; 0.01 c.cm. of a twenty-four-hour bouillon culture injected subcutaneously into a four kilogram rabbit in every instance gave rise to general infiltration at the site of infection, profuse diarrhœa after thirty-six to forty-eight hours and death during the course of the third day. At autopsy the large intestine was found markedly thickened and œdematous (0.5 cm. across), with hæmorrhagic areas over the surface of the mucosa. The contents of the gut consisted of glutinous material mingled with blood. The Shiga bacillus was recovered from the blood and the walls of the large intestine.

The blood of those patients who died during the first few days of the disease did not agglutinate cultures of either the Shiga or the Flexner bacillus, for, as in typhoid fever, the agglutinins do not, in general, appear until the eighth or tenth day. On the other hand, the blood serum of the patients who recovered agglutinated cultures of the Shiga bacillus isolated from the stools, and also the various stock cultures of the same, in dilutions up to 1 in 320. Cultures of the B. coli communis were agglutinated in dilutions of 1 in 40 to 1 in 80. Cultures of B. typhosus were not agglutinated in any dilutions.

2. *Patients Yielding Flexner Bacillus.* In this second group the symptoms and general condition were much less severe than in the former group. Moderately severe colicky pains were present, such as are frequently met with in severe diarrhœas. The stools numbered six to ten per diem and were passed with comparatively little tenesmus; in the more severe cases they consisted, for the main part, of slime mixed with blood. Free blood or portions of diphtheritic membrane, such as characterized the stools in true dysentery, were absent, and the condition yielded to treatment with more or less promptitude. The deaths which occurred in this group were due to causes other than the intestinal condition, for the dysentery in these fatal cases was of the nature of a terminal infection. No pronounced lesions were found in the intestinal mucosa after death.

Like the B. dysenteriæ the Flexner bacillus appears to be readily transferred from patient to patient; it seemed to find favorable conditions for development in cases of pneumonia, meningitis (tuberculous as well as that due to the diplococcus intracellularis), pulmonary tuberculosis and rachitis. In the terminal diarrhœa of these cases the bacillus was invariably found. Flexner has already drawn attention to the fact that this bacillus is frequently met with in the terminal diarrhœa of Bright's disease. The blood serum of those patients who had suffered from diarrhœa for several days gave a positive reaction with cultures of the B. Flexner, whether isolated from the stools of the patients or stock cultures, in dilutions varying from 1 in 80 to 1 in 320. Cultures of the B. coli communis were agglutinated in dilutions up to 1 in 80, but cultures of the Shiga bacillus were not agglutinated in any dilution.

In connection with this group of cases three patients are of interest as indicating a possible source of infection, all the members of the same family. The onset of the disease, which was sudden, occurred about eight hours after eating a preparation of chopped meat which, besides being highly seasoned with paprika and other pungent spices, was indifferently cooked. The parents were less severely affected than the three children, who were admitted to the hospital with severe abdominal pain. The stools were frequent and consisted entirely of slime mingled with blood. A slight degree of fever (99° to 100°) was also present. A smear from the stools when stained by Gram's method showed abundance of bacteria consisting of many bacilli negative to Gram, a few cocci and bacilli which retained the Gram stain. Neither the Gaertner bacillus nor the bacillus enteritidis sporogenes (Klein) could be found, though searched for diligently. But a large percentage of the colonies on the plates proved to be Flexner's bacillus. After the ninth day the blood of these patients agglutinated cultures of the Flexner bacillus, both from their own stools and from those of other patients, as well as stock cultures, in dilutions up to 1 in 320, but did not agglutinate any cultures of the Shiga bacillus. Unfortunately we could not obtain for examination a sample of the meat eaten; the history strongly suggests that that was the source of infection.

3. *Patients Suffering from Summer Diarrhœa.* The clinical picture afforded by the third group of cases was that commonly met with in summer diarrhœa in children. The stools were greenish, with more or less slime, and blood was met with in one or two of the more severe cases. The trouble was apparently due to a variety of bacteria, among the number being B. proteus, B. coli communis of exalted virulence and the pyogenic cocci, especially streptococci. Of interest in connection with this latter organism are the facts brought out from studying a family, several members of which suffered from a diarrhœa which, in the case of two of the children, might have resulted seriously had not prompt measures been taken. The first of the family to be taken was the youngest child, eighteen months old, and the other members were taken successively in order of their ages, the father being the last to fall ill, the mother escaping. The first symptoms were abdominal pain, followed by diarrhœa characterized by frequent stools—eight to twelve per diem—of very offensive odor and consisting of fæcal matter mixed with greenish slime streaked with blood. The temperature varied from 99° to 102°. The second patient was brought into the hospital in a state of collapse, with a subnormal temperature which quickly rose to 103° after application of external heat and stimulants. The other children were less severely affected; the father suffered from diarrhœa for one day only.

The stools of these patients, when examined microscopically, both in the fresh state and after staining by Gram's method, were found to contain vast numbers of chains of streptococci. Bacilli were also present, but in comparatively small numbers. Streptococci and staphylococci were also isolated from the urine of the patients who exhibited the same pronounced constitutional symptoms; 1 per cent. glucose agar plates made from the stools gave abundant colonies of streptococci, cocci and B. coli communis; but neither the Flexner bacillus nor the Shiga bacillus could be found.

The milk supply was suspected of being the source of infection and a sample of this was obtained in a sterile bottle. To the naked eye it had the appearance of being wholesome, but upon microscopic examination it was found to be crowded with bacteria, streptococci predominating. On a glucose agar plate inoculated with 0.1

c.cm. of a 1:10,000 dilution thirty colonies appeared, all but one being streptococci or cocci, and the organisms isolated agreed morphologically with those found in the stools of the patients. Samples of the blood taken on the tenth day gave positive reactions with B. coli communis, but were negative toward both Shiga and Flexner's bacilli.

4. *On the Presence of Flexner's Bacillus in Perfectly Normal Stools.* In the routine examination of apparently normal stools bacilli have in two instances been isolated which, in their cultural characters, have been found identical with the Flexner bacillus, and, moreover, when tested with the various immune sera and the sera of patients belonging to the second group, reacted similarly and to the same degree as did the original stock cultures of the Flexner bacillus. These patients gave a negative history as to diarrhœa and dysentery, and their blood did not agglutinate the cultures from their stools nor the stock culture of B. Flexner in dilutions of 1:40. While these individuals apparently showed no ill effects from harboring the bacillus, it has not yet been proved that they are not a source of danger to the community. On the other hand, it is quite probable that this bacillus finds a lodging place in hosts other than cases of chronic infection; but at present our knowledge of the distribution and nature, especially as regards the domestic animals, of either the Shiga or the Flexner bacillus or of allied forms is extremely limited.

5. *Therapy.* Although Shiga achieved a certain measure of success in Japan by treating cases of dysentery with immune anti-dysenteric serum, yet the results obtained elsewhere from this method of treatment have been anything but satisfactory. Vaccination has been suggested as affording a certain means of conferring a certain grade of immunity. But this mode of prevention, especially in connection with young children, is not likely to be received favorably. Preventive measures in the form of rigid isolation and thorough disinfection of the dejecta in all cases containing blood in the stools would clearly be of the greatest good, as would also be, we need scarcely say, the strict enforcement of regulations regarding the sale of milk and diseased meats. Doubtless the water supply is another fertile source of infection. The

treatment in Vienna is to isolate all cases of dysentery, and the same precautions are taken regarding the disinfection of the stools that are employed in cases of typhoid fever. Serum therapy as it stands at present is not highly regarded. Colloidal bismuth, a new Merck preparation, in doses of 0.5 to 1 gram, given three times a day, was found to be of considerable value. The milder forms of enterocolitis are treated by moderate doses of calomel ($\frac{1}{4}$ to 1 gr.), followed by bismuth subnitrate in doses of 0.5 gram three times per diem. This medication, together with rest in bed and liquid diet of sterilized milk, bouillon, toast, with cocoa or coffee, usually gives good results, except in the cases of terminal infection.

CONCLUSIONS. The study of these cases in Vienna has led us to the following conclusions:

1. Acute bacillary or epidemic dysentery is caused by the bacillus first isolated and described by Shiga in Japan. This bacillus is fairly widely distributed and has been shown to be the active agent in widely separated epidemics.

2. This dysentery proper is accompanied by the formation of diphtheritic membrane, with ulceration of the intestines.

3. The institutional and sporadic or pseudodysentery is caused by the organism first isolated by Flexner, and differing from that described by Shiga in certain constant cultural and agglutinative properties. There are indications that other forms of bacteria exist closely allied to both the Shiga and Flexner types of bacilli and it is possible that these forms take an active part in the causation of intestinal disorders.*

4. Enterocolitis or summer diarrhœa in children (Darmcatarrh) may be caused by various forms of micro-organisms, more particularly by the B. coli communis. The points of distinction, both in the clinical pictures and in the anatomical disturbances, between the diseases set up by these different (non-dysenteric) forms, if they exist, have still to be worked out.

* This paper—and this sentence—was written before the publication of the article by Park, Collins and Goodwin (Journal of Medical Research, vol. xi., May, 1904) calling attention to the existence of a third form, closely allied and intermediate between the Shiga and the Flexner bacilli.

TABLE I.—Biochemical reactions in carbohydrate media of B. dysenteriæ (Shiga) compared with those of other bacilli.

	Dextrose acid, gas.	Saccharose acid, gas.	Lactose acid, gas.	Mannite acid, gas.	Maltose acid, gas.	Galactose acid, gas.	Inulin acid, gas.	Dextrine acid, gas.	Litmus milk. acid, coag, gas.	Remarks.
B. fecalis alcaligenus,	— —	— —	— —	— —	— —	— —	— —	— —	— — —	
B. dysenteriæ (Shiga),	+ —	— —	— —	— —	— —	+ —	— —	— —	1st 24 hrs. 2-3 days + — +	Original culture
B. dysenteriæ (Kruse),	+ —	— —	— —	— —	— —	+ —	— —	— —	1st 24 hrs. 2d-3d dy. + — +	German strain.
B. dysenteriæ from stools,	+ —	— —	— —	— —	— —	+ —	— —	— —	1st 24 hrs. 2d-3d dy + — +	Group I.
B. typhosus,	+ —	— —	— —	+ —	+ —	+ —	— —	+ —	+ — —	
Flexner (Manila),	+ —	2d & 3d days — +	— —	+ —	+ —	+ —	— —	+ —	1st 24 hrs. + — 2d day +	Original culture.
Flexner from stools, Group II.	+ —	2d & 3d days — +	— —	+ —	+ —	+ —	— —	+ —	1st 24 hrs. 2d day + — +	Group II.
Flexner from chronic infection,	+ —	2d & 3d days — +	— —	+ —	+ —	+ —	— —	+ —	1st 24 hrs. 2d day + — +	
B. coli comm. (Escherich),	+ +	— —	+ +	+ +	+ +	+ +	— —	+ —	+ — —	Old stock culture.

TABLE II.—Comparison of agglutinative reactions with immune sera and patient's sera.

	B. coli serum.	B. Shiga serum.	B. typh. serum.	From patients, Group I. Average of sera.	From patients, Group II. Average of sera.	Normal horse serum.
1 : 5120	B. coli comm.					
1 : 2560	.....	Shiga Group.				
1 : 1280	.....	.....	B. typh. stock culture.			
1 : 640	.....	Flexner Group.	B. typh. fresh from stool.	Shiga Group.		
1 : 320	Flexner Group.	.....	Flexner Group.	Flexner Group.	Flexner Group.	
1 : 160	.....	.....	.....	.....	.....	B. coli com. B. Flexner.
1 : 80	Shiga Group.	.....	Shiga Group.	B. coli com.	B. coli com.	B. Shiga.
1 : 40						
1 : 20	.....	.....	....	....	.....	....

We herewith express our sincere thanks to Professor Theodor Escherich for his counsel and for the interest he has throughout taken in the course of our work.

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THE NEOPLASM THEORY OF LEUKEMIA, WITH REPORT OF A CASE SUPPORTING THIS VIEW.

PRELIMINARY REPORT.

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The following paper is a preliminary report of a case, a more elaborate study of which will be published later. It is presented in this form at this time because it is so closely related to the case of chloroma reported at this meeting by Dr. Dock and myself and because it represents an atypical form of leukemia occupying an intermediate position between chloroma and the more usual forms of leukemia. In its essential pathologic features it represents a case of a diffuse lymphadenoid sarcomatosis of the gastro-intestinal tract with metastases in the lungs, heart, liver, kidneys and bone-marrow, accompanied by a leukocytosis of 90,000, 86.6 per cent. of the white cells being atypical mononuclears or polymorphonuclears, and only 1.3 per cent. being neutrophile polynuclears. Clinically the case ran a very acute and malignant course, at first suggesting typhoid, then intestinal obstruction, and with the appearance of a tumor in the right iliac region, finally resembling appendicitis and operated upon as such. The peculiar characteristics of the primary intestinal growth and of the metastases and the fact that the atypical cells found in the circulating blood are identical with those constituting the tumors are regarded as good reasons for the view that the case is to be classed with the leukemias and that the leukemia in this instance is but a phenomenon secondary to the neoplasm and dependent directly upon it.

Without, at the present time, going into an extensive review of the literature, the neoplasm view of the nature of leukemia is as old as our knowledge of the condition. From Virchow up to the present time the majority of writers have noted the striking analogy existing between leukemia (infiltrations and tumor formation) and malignant neoplasms. While within the last decade the infective and toxic nature of the condition has been chiefly discussed, a number of more recent writers (Weber, Pappenheim, Banti, etc.) are bringing into greater prominence the conception of leukemia as essentially a neoplastic hyperplasia of the blood-forming organs, the increase of white cells in the blood stream being a secondary phenomenon.

Banti, in particular, has recently advocated this view. He regards lymphatic leukemia as a *systemic lymphadenoid sarcomatosis of the lymphopoietic and hematopoietic organs*, and myeloid leukemia as a *systemic myeloid sarcomatosis of the hematopoietic and lymphopoietic organs*. His reasons for this view are, in general:

1. The atypical nature of the lymphadenoid or myeloid tissue, both of the bone-marrow and of the secondary foci.

2. The involvement of the vessel walls, particularly of the veins; the destruction of the endothelium and the direct association of the lymphoid or myeloid tissue with the blood stream.

3. The occurrence of both hematogenous and lymphogenous metastases.

4. The fact that the cells of the organs take no part in the formation of the secondary nodules, these arising through the proliferation of the transported cells.

5. The fact that the hyperplasia of the bone-marrow may cause a thickening or a rarefaction of the bone-tissue such as is found in the case of secondary malignant tumors in the bones.

6. The fact that the lymphadenoid tissue may invade the capsule of the lymph glands, while the myeloid may invade the periosteum and periosteal tissues.

7. The cells circulating in the blood are more or less atypical.

The case of chloroma described by Dr. Dock and myself at this meeting presents all these features, viz., a malignant hyperplasia of the bone-marrow infiltrating the periosteum and neighboring

tissues, destroying the bloodvessels and tissues, setting up metastases and giving rise to the presence in the circulating blood of atypical cells similar to those constituting the marrow and periosteal growths and the secondaries. The case which I am now to report briefly presents an atypical sarcoma-like hyperplasia of the intestinal lymphoid tissue, infiltrating and destroying the neighboring tissues, invading the bloodvessels, setting up hematogenous and lymphogenous metastases, and giving rise to the presence in the blood of atypical white cells (leukemia).

The case occurred in the service of Dr. Nancrede, University Hospital Surgical Clinic, and to him I am indebted for the clinical history as here given:

H. J. P., aged thirty years, single, by profession a civil engineer and a teacher, with a negative family history, was admitted to the University Hospital November 23, 1901, in the service of Dr. Nancrede. The patient stated that he had had all the ordinary diseases of childhood, which cannot be proved, since he had no physician during the course of any of these ailments.

Since 1895 he has had several attacks of jaundice, but was never ill enough to stop his work until 1899, when there was a suspicion of malarial trouble, as he had been living in Alabama for several months previous to the attack. He had for years been more or less constipated and neglecting his bowels. Late last September he had an attack of "obstinate constipation," as his doctor told him, with much fever and vomiting; it required from three to four days to thoroughly evacuate the fecal accumulation and he was ill about one week, after which he noticed nothing beyond his habitual costiveness.

On the evening of October 30, 1901, Dr. Darling was called to see Mr. P. and found him in bed, with a slight elevation of temperature, abdominal pain, which was not localized in the region of the appendix and there was no sign of tremor. There was also vomiting. The next afternoon he resumed his teaching. Dr. Darling saw him again December 1st (*i. e.*, the second day after his second attack) and found he had a normal pulse and temperature, but there was some generalized abdominal "soreness" and he was still constipated. Believing that fecal impaction was present, Dr. Darling ordered laxatives and tonics, seeing him on several occasions from this time up to his fatal illness.

Thursday evening, November 21, 1901, he called at Dr. Darling's house, complaining of feeling very ill and having a decided abdominal tenderness. Being taken to the office, examination revealed a mass beneath the right rectus muscle about two inches above the pubes, closely connected with the abdominal wall. By rectal examination a mass was felt in the median line which appeared not to be connected with the intestines. There had been some vomiting; the tempera-

ture was 104°. The urine examination was negative. Laxatives were prescribed, the patient went home on the street car and the next morning had a free movement of the bowels, but his temperature was 103°, his pulse 100 and there was considerable tenderness extending from the tumor toward the right.

He was urged to go to the hospital, where he arrived about 1.30 P.M. November 23, 1901, the temperature being 103° to 104°., pulse 120, and respirations 24. The leukocyte count was 39,000. He looked extremely ill; the pulse was of poor quality; he was dull and did not seem to suffer much. The abdomen was distended and the mass now occupied nearly the whole of the lower portion of the abdomen between the iliac crests, but was less prominent in the left iliac region. The abdominal muscles were moderately tense. For about thirty-six hours there had been marked diminution of the amount of urine, amounting to partial suppression, many granular and hyaline casts, with a few leukocytes, being found in the sediment. The albumin was by heat one-quarter in volume. The day of his death no casts could be found. The only urine secured the day of operation was 70 c.c., specific gravity 1028. During the 24th, only 60 c.c., specific gravity 1026, were passed. The 25th, 500 c.c., specific gravity 1015, were secreted; on the 26th, 780 c.c., with a specific gravity of 1015, were obtained, this last containing a trace of albumin and no casts.

At the time of admission his temperature was 103.3°, falling to 99° the same evening; the pulse was 124, respirations 24. Both pulse and temperature fluctuated widely; the former from 99° to 103.4°, the pulse from 120 to 144. The respirations once reached 30, but usually ranged from 24 to 28. When first seen, and more markedly on admission, he gave the impression of a case of mild typhoid, all his senses seeming dulled, although he was perfectly rational. While manifestly a very ill man, he complained of practically nothing, and when examined showed too little sensitiveness to pain for a normal case of appendicitis of such apparent gravity.

At the operation, performed by Dr. Darling, at Dr. Nancrede's request, a large cavity nearly surrounding the bladder was opened by the usual incision for appendicitis, filled with many ounces of clear, urine-tinted, inodorous fluid. By extending the incision a large mass of small intestine and omentum was found, in which was embedded the greatly swollen appendix, which was removed, but only a small amount of the entangled bowel could be separated. The blood examination on the day of operation showed a leukocytosis of 90,000. No differential count was made at this time.

Vomiting set in after the operation, the ejecta being evidently altered bile and the contents of the upper part of the small intestines, and the emesis continued until his death. Rectal feeding was employed; normal salt solution was given by rectum and skin and the heart's action sustained by strychnin, etc., pain being controlled by codein. The kidneys at first secreted more freely, in the third twenty-four hours 780 c.c. being passed, but very soon they began to lose their activity, despite digitalis. Delirium was present most of the time until

partial and then, finally, complete coma set in, in which latter state the patient died at 5.30 A.M. November 27, 1901.

Autopsy by Dr. Warthin, at 1 P.M., November 27, 1901.

Autopsy Protocol. Body of rather slender build. Abdomen above the level of the ribs. Epigastrium distended. Undertaker's puncture just above umbilicus. Transfusion marks in both pectoral regions and marks of hypodermic injections in both forearms. In the right iliac region a surgical wound, as for appendicitis operation, partly covered with gauze, the gauze extending into the wound opening at the upper half, the lower half being closed by three stitches.

The skin is dark sallow, slightly pigmented over hands and forearms. Over the trunk and upper extremities there are numerous small ecchymoses. The mucous membranes are pale, and present no hemorrhages. Panniculus small in amount. No edema.

Moderate hypostasis over dependent portions. Body heat still present in thorax and abdomen. No evidences of decomposition. Muscles are small, but in fair condition. On section they are dark brownish-red, dry and tough. Slight Zenker's necrosis in the abdominal recti. Rigor mortis is present throughout.

Head and spinal cord not examined.

Diaphragm at fourth intercostal space on the right, fifth on the left. Position of thoracic organs negative. Several enlarged lymph nodes in the anterior mediastinum. Small amount of thymus fat. In it several masses of lymphoid tissue, probably remains of thymus. Pleuræ negative. Pericardial sac thin and lax. Normal amount of clear, yellow fluid. Heart smaller than right fist. Weighs 10½ ounces. Auricles, particularly the right, distended and filled with pale, thin fluid blood and large fat-like, agonal clots. The subepicardial fat is in slight excess. The heart muscle is soft and pale brownish-red in color. The right ventricle wall measures 7 mm., 2 mm. of which are fat. Large white clot in right ventricle extending into the pulmonary artery. The left ventricle wall measures 15 mm. The valvular orifices and flaps are entirely negative.

No fluid in pleural cavities. Left lung weighs 19½ ounces; right one, 29 ounces. Pleuræ of both lungs entirely free. Both voluminous. The upper lobes pale red and largely air-containing; the lower lobes markedly hypostatic. Lower left lobe shows bands of anthracosis corresponding to the ribs. On section it is edematous and presents a mottled surface, the mottling in part being due to greatly dilated vessels filled with partly coagulated blood. Throughout the right lung there are soft and friable yellowish areas slightly elevated above the surface. On pressure they yield no pus. Small, dark-gray, airless areas are also present throughout this lung. The bronchi are filled with a slightly cloudy, foamy exudate. The mucosæ are injected. The bronchial glands are swollen and edematous, and are heavily anthracosed. The pulmonary arteries contain white, agonal clots; the veins are filled with red jelly clots.

The pulmonary artery and aorta both show slight sclerotic changes in the intima. Thoracic duct is negative. Mouth and neck organs not removed. Thyroid negative. Esophagus negative. Cervical glands not enlarged.

On opening the abdomen the transverse colon is greatly distended, lying just above the umbilicus. The lower border of the stomach in the median line is four finger-breadths below the ensiform. The liver is pushed upward and backward. The omentum is deeply congested, poor in fat and rolled up to the level of the umbilicus. On the right it sends a prolongation down to the appendix region. In the omentum are several enlarged lymph glands, which, on section, are homogeneous, white and soft. The peritoneal cavity contains about 300 c.c. of a brownish fluid smelling of formalin. Below the umbilicus the intestines are adherent to the anterior abdominal wall and to each other by rather firm adhesions composed of blood clots and fresh fibrin. These adhesions are easily separated. They increase in number and size toward the right iliac region, where there is a firm tumor mass, consisting of the greatly thickened mesentery of the ileum and of several loops of ileum firmly adherent to each other by partially organized adhesions. The mesentery of these folds is greatly thickened and contains enlarged lymph glands. The entire mesentery is indurated. On section the indurated tissue is firm, white and tendon-like, but yields an abundant cell juice on scraping. No evidences of pus found in the tissue and nothing resembling tubercles.

The intestinal wall, with the exception of that of the large intestine, is greatly thickened, firm, and on section resembles the indurated mesentery. The duodenum is greatly distended and filled with a thin, bile-stained fluid. The mucosa and muscularis are thickened (5 to 20 mm.), and on section firm and white. Jejunum and ileum filled with thin, bile-stained fluid. The entire wall of the small intestine is greatly thickened, the induration involving chiefly the submucosa and mucosa. On section these are white, nearly homogeneous and firm. In those coils of ileum involved in the tumor mass the intestinal wall is enormously thickened, on section presenting the same characteristics as the mesentery. The surface of the mucosa shows large, shallow ulcers, very irregular, extending entirely around the lumen and covered with grayish exudate. Occasional nodules present into the lumen; on section these are white or yellowish in color, resembling the nodules found elsewhere.

The stump of the *appendix* shows the same induration. Measures 2 cm. in diameter. Ligatures in place. The mucosa of the large intestine shows a much less marked infiltration.

The *stomach* shows a greatly thickened mucosa, especially in the fundus, where it is about four times as thick as normal. On section the thickened mucosa is white and firm. The surface of the mucosa is dark red in areas and shows numerous small ecchymoses. In many places the induration involves the entire stomach wall, which on section is firm, white or yellowish and nearly homogeneous.

The *spleen* weighs 11½ ounces. Larger and more round than normal. Capsule covered with fine fibrin threads. Consistency soft. On section brownish-red; cut surface bleeds freely. Follicles not seen. Cut surface nearly homogeneous. One small hyaline body in pulp, size of large pinhead. In the gastrosplenic omentum there is a small accessory spleen, with greatly thickened and hyaline capsule.

The *adrenals* are fairly well preserved and present no pathologic changes.

The *left kidney* weighs 7 ounces. Fatty capsule poor in fat. Fibrous capsule slightly adherent, especially over small, yellowish, elevated nodules in the cortex. Surface of the cortex mottled reddish-blue and yellow. Veins moderately congested, Throughout the cortex there are numerous nodules, in size from that of a pinhead to a cherry, elevated above the surface, yellowish and very soft. On section they appear somewhat wedge-shaped, the base toward the cortical surface. They are rather sharply outlined, although some of them show a zone of infiltration into the surrounding kidney tissue. The nodules possess no red borders, but some show minute hemorrhages throughout their substance. Their cut surface is nearly homogeneous and of uniform consistence. No pus can be expressed from them and they show no central softening. Scraping yields an abundant cell juice, consisting almost wholly of cells resembling large lymphocytes. Numerous mononuclear eosinophiles and some nucleated reds are also present in the scraping. Cortex measures 10 to 15 mm. The pelvis is greatly dilated, mucosa thickened and shows small ecchymoses.

The *right kidney* is similar in all respects to the left. It weighs 8½ ounces. The nodules are more numerous and, as a rule, larger than those in the left. The parenchyma of both kidneys is cloudy.

Both *ureters* are dilated and filled with cloudy urine. They are compressed at the brim of the pelvis by the indurated retroperitoneal tissues. Bladder contains a small amount of cloudy urine. The mucosa is thickened and contains scattered ecchymoses.

At the external meatus there is a slight papilloma, and there is a small double varicocele, otherwise the external and internal *genital organs* are negative.

The *liver* weighs 4 pounds. Larger than normal. The capsule is negative, with the exception of a few small areas of fibrinous exudate. On section the parenchyma is pale, the central veins containing small amount of blood. The consistency is increased and the cut surface is more translucent and glistening than normal. The peripheral portions of the lobules are pale yellow. The connective-tissue trabeculæ are more distinct than usual, appear enlarged and contain numerous small, yellowish-white nodules, size of a pinhead to that of a pea, similar to those found in the lungs and kidneys.

The *gall-bladder* is negative.

The *portal vein* negative.

The examination of the *pancreas* reveals nothing pathologic.

The *mesenteric glands* are enlarged, particularly those corresponding to the

loops of the ileum involved in the tumor mass; many are as large as pigeons' eggs. On section they are white, homogeneous and soft.

The *retroperitoneal glands* are enlarged. Only one *hemolymph node* could be recognized with the naked eye. All the other glands are white, soft and homogeneous on section.

The long bones show no increase of *red marrow*. Marrow of ribs and vertebræ is apparently normal red marrow. In the red marrow of the sternum there are a few grayish areas of softer consistence, suggesting small secondaries.

The *axillary, cubital, inguinal* and *cervical lymph nodes* not enlarged.

Microscopic Examination. *Blood.* About twenty smears of blood were obtained through the kindness of Dr. Lambley, one of the surgical internes. About one-third of these had been obtained on the patient's admission to the hospital, November 23d. At this time the leukocyte count was 39,000. No differential count was made at the time. The remaining smears were obtained on the day of death, when the leukocyte count was 90,000. The smears were fixed partly by alcohol and ether and partly by heat. The latter fixation was not very satisfactory. Hematoxylin and eosin, methylene blue and eosin and the triacid stains were used. Four of the smears were given to Dr. Dock for examination and his report is here given:

Examination of Blood from the Case of Mr. P., November 26, 1901. (Dr. Dock.)

The examination was limited to four covers. One of these was fairly well fixed and stained with hematoxylin and eosin; the others were badly spread, not very well fixed in ether and alcohol. Two of these were fixed over by heat for the triacid stain, but did not give very good results. The third stained fairly well in eosin and methylene blue. The general features were alike in all specimens. Differential counts were made of all, but it was not possible to get a large number in consecutive order, except in the case of the first-mentioned preparation. From this one 2000 leukocytes were counted.

Red Blood Corpuscles. These are apparently not much below the normal number; size and shape well preserved. Normoblasts and megaloblasts are found in all the preparations. With the 2000 leukocytes there are three typical normoblasts, three typical megaloblasts and five free nuclei. A few other megaloblasts in other parts of the preparations have degenerated or fragmented nuclei.

Leukocytes. These are much increased in number. The differential count of the first-mentioned cover differs from that of the other three in having more of the pathologic cells described below and correspondingly fewer of all other forms, the difference of the former being 10 per cent. 10.5 per cent. have the characteristics of lymphocytes, 2.5 per cent. being the size of or smaller than red corpuscles, 8 per cent. larger. The nuclei of all of these are usually simple, but

sometimes incised on one side. A few show imperfect fragmentation of the nucleus. The protoplasm is usually scanty, but more extensive in proportion in the larger specimens. It takes diffuse stains, sometimes deeply, sometimes hardly at all, but shows no granulations.

Polynuclear leukocytes, with neutrophile granules, are present to the extent of 1.6 per cent. (In smaller counts in imperfect preparations, 3 per cent.) Aside from the low count, they offer no points of interest, being of average size. They can be readily distinguished from the other polymorphonuclear cells mentioned below.

Normal eosinophile cells number two per mille.

Mononuclear eosinophile cells are more numerous—five per mille. They are of about the same size as normal eosinophiles, the large and small forms so common in myelogenic leukemia, being so rare as to escape counting. Myelocytes of Ehrlich can be found in the triacid preparations in about 2 per cent. They do not appear in the count of 2000 leukocytes. It is possible that some of the pathologic cells described below in that count have neutrophile granules, and should be counted as myelocytes, but the forms so common in ordinary cases of chronic myelogenic leukemia are certainly very rare.

Degenerated leukocytes are present to the amount of 5 per thousand. One of these is a polymorphonuclear eosinophile; the others show only degenerated nuclei, without definite outlines.

The rest of the cells, 86.6 per cent. of all leukocytes, vary considerably in detail, but have certain features that make it convenient to count them together. They include a few cells that in ordinary counts would be classed as large mononuclear or transitional, but there are all stages from these to the more unusual cells mentioned below. Some have round or elliptic nuclei, with a narrow or wide rim of protoplasm. Many have triangular or imperfectly round or elliptic nuclei, but in most the nuclei are either incised in one or more places, or kidney-shaped, or with two unsymmetric lobes, or like saddle-bags. Many nuclei are indescribably irregular and in some of the larger forms they often look like two or three swollen nuclei from polynuclear neutrophile cells, fused together at the ends, or sometimes covering one lobe over another. These nuclei do not stain as deeply as those of the normal polynuclear cells, but about as deeply as those of the larger lymphocytes or of myelocytes (of Ehrlich) in leukemic blood. The chromatin is usually diffuse, but sometimes shows a coarse network. In general, granules cannot be brought out in these cells, either by the triacid stain or eosin, but a few of them show granules, very fine, with the triacid or eosin.

Mast-cells do not seem to be present, but, unfortunately, they were not stained as thoroughly as could have been desired.

The remaining smears were studied by the writer; but without at this time going into an elaborate description of the findings, it will be sufficient to say that they, in general, correspond with the report given by Dr. Dock. The differ-

ential counts varied somewhat with the smear. Between 80 and 90 per cent. of the white cells were atypical mononuclears and polymorphonuclears, as described above, and of these the writer would class about 50 per cent. as corresponding to the atypical "large lymphocytes" seen in the chloroma case. In some of the atypical mononuclears a neutrophile granulation was present, and in a few eosinophile granules.

From the great number of white cells in the blood, the replacement of the normal polynuclears by atypical mononuclears and polymorphonuclears and the great variety of cell form, the case must be regarded as one of leukemia and classed as an atypical lymphocytic leukemia.

Appendix. The appendix removed at the operation was greatly thickened, 2 cm. in diameter, hard and on section showing a greatly thickened wall, white and nearly homogeneous. On microscopic examination the mucosa and submucosa were densely infiltrated with round cells, the infiltration extending into the muscle coats. There was a distinct new-formation of reticulum and the cells for the greater part have a protoplasmic body and round, oval, incised, saddle-bag or polymorphous nuclei. Numerous mononuclear eosinophiles are present. In general, the picture is that of an infiltrating, lymphadenoid sarcoma.

Autopsy Material. I shall omit a full description of the microscopic findings and give only the most essential points. In general, the microscopic picture is that of a lymphatic leukemia, the bloodvessels containing great numbers of white cells, the majority being of the atypical mononuclear and polymorphonuclear forms described above. In the case of the liver the connective tissue of Glisson's capsule shows the infiltration characteristic of leukemia and similar infiltrations are present in the other organs. Sections of the wall of the ileum, jejunum, duodenum and stomach show that the mucosa and submucosa, and in some places the muscularis, are replaced by a diffuse growth in general resembling a lymphosarcoma. This tumor infiltration is most marked in the ileum and becomes less as the distance from the ileum increases. In the latter location the growth shows a rather dense reticulum, the spaces of which are filled with cells of the type of large lymphocytes. Numerous mononuclear eosinophiles are present. The growth is fairly vascular and the cells show a marked tendency to invade the vessels and themselves form the wall. Nearly all trace of the normal elements of the wall are lost, but in the upper part of the small intestine and in the stomach the tumor cells can be seen infiltrating the muscle, which is still preserved. In the stomach remains of the gastric glands are present in the masses of round cells. Sections of the mesentery and mesenteric glands show a tumor infiltration of the same character. It may be mentioned here that the sections from the ileum and the mesentery bear a striking resemblance to the section of the periosteal infiltration in the case of chloroma, but do not show such a high proportion of eosinophiles.

The firm, yellowish or white nodules seen in the kidneys, lung, liver, bone-marrow, etc., present the same microscopic characteristics as the primary growth

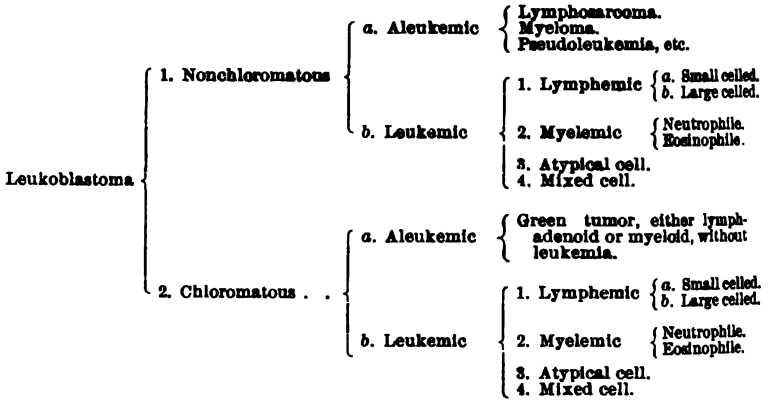
and are regarded as metastases of the same. Smaller ones were found microscopically in the heart muscle. Sections of the spleen presented the appearances of a lymphoid hyperplasia of the pulp. Sections of the red marrow showed an increase in the number of cells of the large lymphocyte type. Liver and kidneys show parenchymatous degeneration.

Smears of the tumor of the ileum show a preponderance of cells of the same atypical character as those found in the blood.

Careful study of the case leads to the following diagnosis: Primary lymphadenoid sarcomatosis of the ileum; metastases in kidneys, lungs, etc.; atypical lymphocytic leukemia; parenchymatous degeneration of kidney and liver.

This case therefore, like the chloroma case, presents a definite tumor formation, having all the characteristics of malignant neoplasms (infiltration and metastases) and associated with a leukemic condition of the blood, the white cells present in the circulation being of an unusual type, and for the greater part corresponding to the cells of the tumors. I regard this case, therefore, as well as the case of chloroma, as offering strong evidence for the neoplastic nature of leukemia. It becomes evident then that the blood condition is purely a secondary phenomenon, and does not in itself throw any light upon the location of the tumor process. Leukemia must be regarded as a *neoplastic hyperplasia of the parent cells of the blood cells.* Such hyperplasia may exist without a leukemic condition of the blood (aleukemic leukemia). The white cells produced by the hyperplasia are more or less atypical, and are less resistant than the normal leukocytes, hence their rapid disappearance in intercurrent infections, *x*-ray treatment, etc. On the other hand, they resemble the normal white cells to such an extent that they cause but little reaction on the part of the tissues which they infiltrate.

Inasmuch as the term leukemia has come to be identified with an increase of the white cells in the blood stream, the designation of *leukoblastoma* might be applied to the essential disease process—the hyperplasia of the parent cells of the blood cells. It must not be forgotten, of course, that the ultimate *Anstoss* of this atypical hyperplasia is not yet known, but that we are here in the same position as in regard to the etiology of malignant tumors in general. The following scheme is offered as a simple classification of the disease:



It is evident that a leukoblastoma could arise in any part of the body in which the parent cells of blood cells are present. The variety of cell form in the resulting leukemia would depend not upon the location of the primary hyperplasia, but upon the degree of differentiation of the cells arising from this hyperplasia. The old classification of leukemia into lymphatic, myelogenous, etc., loses its force if based upon the blood picture, and, as mentioned above, it is obvious that the latter does not necessarily reveal the site of the primary growth.

A CASE OF UNCOMPLICATED HYSTERIA IN THE MALE LASTING THIRTY YEARS, WITH POST-MORTEM EXAMINATION.

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AND

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DESCRIPTIVE HISTORY BY DR. MITCHELL.

In the *American Journal of the Medical Sciences* for October, 1876, were described a number of forms of spasms which I called functional, after the term employed by Duchenne de Boulogne.

In these cases normal movements caused or intensified certain spastic phenomena. Among these examples I briefly noted the case of Robert Connolly, which is, for many reasons, so remarkable that I propose to reprint it at length. It has passed during thirty years under the eyes or care of the present writer, of Drs. Sinkler, Lewis, Spiller, Dercum and John K. Mitchell. All of these neurologists agree as to its being a typical example of hysteria in the male. Whether through hysteric interests and the vanity of being thought unusual, or because I had been able to serve him in various ways, he volunteered to leave me his body. Within a few hours after his death I made free to use this privilege. There had been meanwhile no intercurrent malady, nothing to disturb such pathologic states as hysteria might offer. The death was sudden. The conditions seemed to be ideally perfect. This unusual chance was fully utilized. I am aware of no other case of uncomplicated hysteria in which the search for causative lesions seemed to offer such an opportunity. Its unique importance excuses the length of my report.

In the winter of 1876 Robert Connolly applied for treatment at the clinic of the Infirmary for Nervous Diseases.

Mr. C., white, watchcase-maker, aged thirty-three years, married, no children, of the utmost sobriety and until 1876 a moderate smoker, now does not smoke. His grandfather, mother and two maternal aunts had hemiplegia in middle life. His father was healthy and died at eighty-three. Two of five sisters of Mr. C. were insane, a third had hip disease, an uncle had epilepsy, a cousin paralytic dementia.

As a child, and indeed through life, Mr. C. was nervous, timid, gentle, reserved and although slow at his lessons was not lacking in intelligence. At seventeen he had typhoid fever, without complication or sequels. At twenty-three he fell twenty feet without serious results. At twenty-five he had sunstroke and was insensible for two days, but had no consequences except a life-long oversensitiveness to sun-heat. At twenty-nine he began to have some difficulty in his delicate handwork. This was at one time a weakness of either hand and at another a momentary spastic condition. I may here add that he was ambidextrous. The hand trouble came and went.

On Decoration Day, 1874, he grew excited and emotional after witnessing the ceremonies and on the way home became of a sudden for a few minutes so weak in the legs as to have to sit down on a doorstep. From time to time this recurred, but with less severity. He became weak, stood still, felt a return of power and walked on. With these attacks came also pain in the lumbar region and the first of the cervical pain felt at times ever since.

In January, 1875, began inconstant, rather fine tremor of the left hand, only visible when the arm was flexed.

The patient when first seen by me was a rather thin, pallid man, with a nervous, uneasy, anxious look. He was a person of unusual refinement, very gentle and timid, but clearly intelligent and well pleased to be considered as an uncommon case and overwilling for a time to exhibit the symptomatic spasms. Then abruptly his face would change, he would lose his constant smile and be annoyed by our curiosity.

He had at this time no organic trouble. His digestion and bowels were in good order, his senses perfect, nor had he then or later any of the ocular phenomena of hysteria. His sleep was good. The tremor of the left arm by degrees attained greater amplitude and gradually, during the next three months, he developed the symptoms noted by Dr. Sinkler, at that time my clinical assistant.

In sleep there was no movement; when he awakened he was conscious of the left hand being rigidly closed. In a few moments it began to twitch, the fingers moving as do those of a violin-player. The slightest movement of any other limb, or the act of speaking or eating, caused the left arm to execute a constant motion of striking the bed or his side, the limb being meanwhile extended. When he arose and walked this action became more violent and so

much resembled the steady, rapid movement of a pendulum that I spoke of it to my assistants as a case of what might be called, descriptively, pendulum spasms. In fact, its rhythmic regularity was astonishing. Dr. Sinkler timed it, on one occasion, as 157; and on several others I found it always 160. It was as accurate as the heart in its motion, but certain things increased either the power or the number of the movements. Thus, if he stood up, after having been seated, the number did not alter, but the force of the blow on the thigh increased remarkably.

If while standing he elevated and extended the right hand and arm to the shoulder level, instantly the rhythm mounted to 200, and when the right arm ceased to act the number fell again to 160.

When there was no pendulum spasm he could perform with the left arm any voluntary act not involving the hand, which itself never ceased to twitch; but while the swinging spasms lasted he could execute with it no volitional act and effort to control the limb enormously increased the spasms. Excitement and emotion and all forms of electricity added to the force of the motions, but voluntary movements of other limbs increased the number more than the force. Attempts passively to fully extend his partially flexed fingers caused increased pain in the occiput, just as the effort to overcome rigid gastrocnemii in some cases gives rise to pain in the dorsal spine. He had power to stop the spasms by certain maneuvers. If he seized the left hand by the right, and flexing the left arm, held it, the left hand for a moment seemed to struggle with increasing violence; he tottered, his face became convulsed; there was horrible pain in the back of the head. Then as he gently released the left arm, save for a slight tremor or twitching of the unquiet fingers, it remained at rest and might not move in violent spasm for an hour or more and was sometimes nearly still for twelve hours. He avoided the use of one hand to stop the other, because of the great pain it caused in the head. When he stopped the hand by catching it under his leg, he had little head pain, but it was so unpleasant for him to stop it that he rarely did so.

When standing, if he wished to check the pendulum spasm, he threw the left leg back so as to trip the toe; the arm then fell in toward the right and he brought the leg forward, catching the arm against the thigh. Then there was a general convulsive movement of the entire body and the limb came to rest.

When the arm was hanging at his side it began to move if he walked a few steps, or if he lifted the right arm, in which at times, especially after sudden arrest of the spasm, I noticed some large tremor. In all of this strange set of symptoms there was no loss of consciousness, no anesthesia, no speech or ocular trouble, no aural defect. When he walked long or fast the legs had some disposition to become rigid, but this was an inconstant feature.

The pendulum spasms continued unchanged up to October, 1876, when they ceased quite suddenly and he began to have rotatory movements. The

extended left hand and arm described a circle at the rate of 140 a minute or more. Later, the rate increased, but as these motions are fully described in Prof. Dercum's notes I leave to his account the details. Henceforward Mr. C. was subject to one or the other of these forms of spasms. From August, 1895, he had at times long periods of chronic contraction of the fingers of the right hand. The contraction relaxed when the member was held up above the head by an assistant, but this position gave rise to a wild convulsive motion in both arms. When an observer seized and firmly held the swinging arm, a general convulsion followed, involving in succession the other arm, face, neck and legs.

From the autumn of 1876 and thereafter all movements ceased when he lay down, but recurred on his standing up and were exaggerated by walking. If, however, when lying down he lifted his head, the left arm began to beat on the bed and did not cease until he stood up and then lay down again. Tapping the muscles smartly while he was supine caused no movement until the quadriceps tendon on the right was struck below the patella. The usual K. G. followed and then the left hand first and next the right flexed and remained in spasms a few moments. A tap above the knee occasioned no such spasm.

Volitional effort at control made the spasm worse. At this period all the muscle-muscle reflexes were excessive, but there was no clonus. The skin-muscle reflexes were present throughout and normal. All electric reactions were normal.

There are some later notes in which he is spoken of as having at times pendulum movement and at other times rotatory motions. The tremor varies, comes and goes and is chiefly in the right arm.

In 1896 and later he had sometimes for a month retention of the urine and need to have the water drawn by catheter, but at no period was there ever cystitis or prostatic enlargement. There had been no retention of late, but at times he had scanty urine, the quantity falling to six or eight ounces in the twenty-four hours.

In 1888 I turned over my patient to Prof. Dercum for study and photographic records were made with the aid of Mr. Muybridge. As these photos do not help to understand the case any better than do Dercum's clear descriptions, I have not reproduced them in this paper, but refer the curious to the work on *Animal Locomotion* published in 1888.

After quoting my account of the case as seen in 1876, Dr. Dercum writes as follows:

"The phenomena presented have undergone some changes. The simple pendulum movement is now replaced by a more complex rotary movement and which is present only under certain conditions. Thus, when Mr. C. is sitting or standing still, the arm is carried in a semiflexed position, while the hand and fingers are markedly contracted and in constant vibration. Were it not for this last factor, namely, the vibration, the position would bear some

resemblance to that assumed by patients suffering from secondary contracture.

"If, however, Mr. C. attempts to rise or walk, the forearm becomes slightly less flexed, whilst the vibration increases both in amplitude and rapidity. If the walk be persisted in, and be it ever so slow and gentle, the forearm finally becomes completely extended and now the entire arm describes a rotary motion, such as is shown in the upper series of Plate 557.[1] It will be observed that this movement is one in which the hand, while it is suspended from the shoulder like a pendulum, describes a circle by first sweeping forward, then outward, then backward and finally forward again to its original position. If now, while the arm is performing this peculiar movement, Mr. C. attempts to raise the arm up to the shoulder even the rotary movement increases wonderfully in extent. The arm describes a circle. The arm extended, and the hand and fingers contracted, sweeps over a circle in front of the body. The hand sweeps upward and outward and then inward again to its original position.

"At the same time that this spasm of the left arm is taking place the right arm, too, becomes convulsed. It is raised abruptly and the forearm directed upward and a series of to-and-fro movements begin, which examination shows are synchronous with the rotary movement of the opposite limb. As the rotating limb rises, the right arm rises; as the former descends, the latter descends. As the left arm sweeps inward and upward, the right arm steadily ascends; as the left arm goes outward and downward, the right arm steadly descends. There is certainly here a curious association of movement. If instead of raising the arm to the shoulder Mr. C. simply sharply flexes the left forearm at the time it is rotating a series of to-and-fro movements replace the rotary movements. That is, the left arm is thrown violently backward and forward. At the same time the right arm becomes similarly affected and it, too, is thrown violently backward and forward. As in the previous experiment, the movements are found to be synchronous. It will be observed that at no time does the right hand become contracted and the fingers clawed.

" Some idea may be gained of the rapidity of these movements when we reflect that the complete cycle of the movement occupies less than the half of a second (represented in Fig. 19),[1] while in Fig. 20[1] the rapidity had so much increased that the cycle occupied only the third of a second.

" If Mr. C. is sitting quietly in a chair, with the arm in a semiflexed position, already described, then lies down with his back and head flat on the ground, all vibration in the hand ceases. It becomes perfectly quiet and he can execute with it most exact and delicate voluntary movements. If, however, he now attempts to raise the head, violent tremor at once appears in the hand. This tremor is so violent that the feet and head are affected. It is remarkable that the raising of the head is the only movement that provokes the tremor. Raising the right hand or either foot does not have any effect. Similarly, if he lies upon

[1] See Dercum on Animal Locomotion for the plates.

the ground and the motion be completely arrested, it is again violently excited by striking the patellar tendon or by attempting to elicit ankle clonus. It is also a remarkable fact that the tremor so excited, or excited by raising the head, cannot be quieted unless Mr. C. arises completely from the ground and lies down anew."

I have seen Mr. C. from time to time since 1898. In these later years there was no change of moment, but he was certainly stronger and when in the country walked five or six miles daily. The pendulum movement was not often observed and the weakness of the legs never returned. The rotation action persisted, as described, until his death. In July, 1903, he presented symptoms of cardiac weakness and was under Dr. Sinkler's care.

Increasing palpitation and shortness of breath occurred in October. November 11, after breakfast, he went to the water-closet and there suddenly died.

The treatment of this case is of interest. He saw many doctors and haunted clinics and was variously treated, with no good result. In December, 1897, I asked Dr. J. M. Taylor to hypnotize Mr. C. and use suggestion, a previous attempt by another assistant having failed. As usual, Mr. C. took a freshly hopeful interest in the new treatment and kept a pencilled, irregular record of the sittings and their results. For a long while it was impossible to induce the hypnotic state, but, as Dr. Taylor writes me, after thirty sittings, of a half-hour each, partial effects were attained. During these many sittings Mr. C. never passed into deep sleep, nor did he lose any sensory perception. Mr. C.'s notes state that after the seventh sitting he wrote a letter with his left hand and without tremor. On the twenty-third sitting the pendulum movements, previously very active, ceased for a few hours. This effect was obtained thereafter only at intervals during daily hypnotization. In January the sittings were more successful and on the fifteenth sitting in that month all spasms ceased. He was able to take a place as assistant in the Jefferson College library and for three months continued well, efficient and much liked for gentleness and amiability. Then something took place which excited him disagreeably and at the same time he had influenza. The spasms returned in both forms.

While he was in bed Dr. Taylor visited him and was able so to influence him by an order that he could rise and walk about the room without spasmodic actions. It is interesting that after this he declined to be aided again by hypnotic means, declaring to Dr. Taylor that the hand of the Lord was upon him and that he felt he should bear his trouble with a serene mind to the end of his days. Whether this was the result of a temporary mood or was one of the self-delusive states common in hysteria, I am not sure. Once, however, he allowed me to hypnotize him, with good results, which were not lasting, but after this would have no more of it nor give a reason except that it was disagreeable. Probably he missed the attention his case excited, for now again he began to appear at clinics, but was unwilling to take any form of treatment.

It is needless to say that every other means of treatment had been sedulously employed and that, excepting hypnotic suggestion, all had failed.

On the day of death the post-mortem section was made by Drs. Eshner and Allen, with the assistance of Prof. Spiller, to whom was confided the study of the nerve organs.

Cervical Region. Sections from the lower part of the cervical enlargement of the cord stained by the thionin method are normal. The chromophilic elements of the nerve cells of the anterior horns stain well. The nerve cells are pigmented, but not more so than is usual in a person advanced in years. The nerve cells of the anterior horns are numerous and equally so in the two sides of the spinal cord. The white matter of the anterior, lateral and posterior columns is not degenerated. The anterior and posterior roots are normal. Anterior roots from the right side of the cervical region were cut separately from the cord so as to obtain a large number for examination. These roots are perfectly normal. Sections from the midthoracic region are normal.

Lumbar Region. The nerve cells of the anterior horns by the thionin method are like those of the cervical region and are normal. The white matter of the anterior, lateral and posterior columns and the anterior and posterior nerve roots are normal.

Brain Cortex. Sections were taken from the middle of the precentral convolutions of the left and right cerebral hemispheres. The nerve cells are numerous and well stained by the thionin method, and appear normal. No distinction can be made between the sections from the right and left hemispheres. Sections stained by the Weigert hematoxylin and acid fuchsin with hemalum are normal. The tangential fibers are numerous in all the sections from the cerebral cortex.

No signs of meningitis or of cellular infiltration are found anywhere in the brain or cord. The right precentral convolution is remarkably well developed and more so than the left precentral. It would be well, however, not to attribute too much importance to this. All the convolutions of the brain are well formed.

The microscopic examination of the brain and spinal cord reveals nothing that could be regarded as distinctly pathologic and affords no explanation for the involuntary movements.

COMMENTS BY DRS. MITCHELL AND SPILLER.

Remarkable, indeed, were the involuntary movements in the left upper limb in this case, persisting through so long a period, and it may at first thought seem strange to those who have not given much attention to the pathology of the nervous system that no lesions have been found to explain them; and yet we could hardly expect spasms that could be held in check for some time by hypnotism to be dependent on organic changes in the nervous system.

While we cannot cite a similar example with an equally long duration, we may refer to other forms of involuntary movements in which the findings have been negative. Numerous lesions have been found in cases of the so-called idiopathic epilepsy, such as sclerosis of the cornu ammonis, the cortical sclerosis of Chaslin, the alteration of certain layers of nerve cells, etc. But all these lesions are of more or less doubtful value and it is questionable whether they in any degree explain the convulsive movements. The epileptic spasms associated with unconsciousness and attended by alteration of the blood pressure and possibly toxic conditions are usually so severe that at least some, if not all, of the lesions found in epilepsy may be the sequent results of a long succession of these serious attacks.

The pathology of chorea has not yet been determined if we except the form of Huntington, in which mental symptoms are prominent and the movements are only a part of the symptom-complex. We do not overlook the fact that certain lesions have been described as occurring in Sydenham's chorea, viz., slight thickening of bloodvessels, small hemorrhages, some round-cell infiltration, "chorea-bodies," even micro-organisms, etc. The pathology of chorea, so far as it is understood, has been presented recently by Hudovernig, but we trust that we may be pardoned skepticism as regards the importance of these findings in chorea.

We should expect to be more successful in a search for lesions in convulsive tic, as this is in most cases a more serious affection than Sydenham's chorea, and yet, so far as we know, the pathology of convulsive tic has not been determined.

No organic changes in the nervous system have been discovered to throw any light on the nature of hysteria, even though involuntary jerkings or contractions have persisted a long time.

We might expect to find organic changes in the remarkable affection known as paramyoclonus multiplex. J. Meinertz[1] has described recently a case of myokymia, by which is meant contraction of muscle bundles, fibrillary contractions, without organic disease.

[1] Neurologisches Centralblatt, February 1, 1904, p. 101.

It differs from the paramyoclonus of Friedreich in that in the latter each affected muscle contracts as a whole. Meinertz suggests that in myokymia the nerve cells of the anterior horns of the spinal cord may be in a condition of increased irritability, and mentions that others have entertained the same view, and that Friedreich was inclined to attribute the involuntary movement in the disease described by him to this cause. Meinertz believes that this increased irritability of the nerve cells of the anterior horns may exist without causing any alteration that can be detected. Such a theory naturally cannot be refuted, nor can it be proved and it seems most improbable. An abnormal condition of nerve cells sufficiently intense to cause such pronounced movements of the muscles would, in course of time, be likely to lead to organic changes detectable by the microscope.

Recently J. R. Hunt[1] has made a careful examination of the material from a case of Friedreich's paramyoclonus multiplex and he mentions that pathologic anatomy has thrown no light on the subject of this disease. No evidence of pathologic change was discovered by Hunt in the brain and its meninges or in the spinal cord. The nerve cells of the anterior horns and of the cerebral cortex were normal. The peripheral nerves, the intermuscular nerve fibers and the muscle spindles also were normal. The muscle fibers were increased in size and sarcolemma nuclei were found between the sarcous elements. It is well to be cautious in attributing much importance to these changes in the muscles. Hunt refers to Friedreich's case in which the histologic examination of the spinal cord and biceps muscle was made by Schultze. The findings were negative. This and Hunt's case seem to be the only examples on record of this type of paramyoclonus multiplex with systematic histologic examination.

In Mr. C.'s case the heart was the only organ which was plainly diseased, and it presented some unusual conditions, of which Prof. Allen Smith gives the following description:

"The heart when brought to me was in formaldehyde, already partially dissected. It weighed 400 g. The left ventricle, the special seat of enlarge-

[1] Journal of Nervous and Mental Disease, July, 1903, p. 408.

ment, is described largely from dissection. The wall of the left ventricle at base (the thickest part) measures 2.5 cm.; of right at corresponding position, 8 mm. Near the apex of the left ventricle on the superolateral convexity is an area a little larger than a dime, which externally shows white and somewhat depressed, as from a scar. The wall in this area is not above 5 mm. in thickness, dense and fibroid to palpation. Corresponding to this area and for a considerable zone about it the endocardium, involving that of the pectinate and papillary muscles, is white, opaque and at its thickest part fully 2 mm. thick. In dissection of the coronary artery to this part its wall is found generally thickened and fibroid and is lost as a tiny, thread-like branch in the cicatrix (not cut lest connection be lost, but apparently solid). The wall of the ventricle in the entire apical portion is decidedly diminished, on an average to about 8 mm.; while with a rather abrupt border toward the base the previously recorded excessive thickness is reached. The muscle toward the base is apparently normal so far as gross appearances are concerned; in the thinned area it is paler and firmer than normal. The sheets of the aortic and mitral valves are decidedly sclerotic and opaque, those of the aortic opening showing advance of sclerosis from base toward free margin. The valves of the right heart and endocardium of the cavities are normal. The cardiac openings could not be estimated because of their previous section. The aorta in the coronary sinuses, about the arterial openings and along the attachments of aorta cusps, shows slight patches of advance atheroma.

"Microscopically, sections through the wall, close to the dense cicatrix, show the pericardium and endocardium much thickened and the latter in places very dense and hyaline. There is slight fatty infiltration in the pericardium. The myocardium in places is almost completely cicatricial; but much of the several sections shows the presence of muscle bundles surrounded by a large amount of connective tissue. Some of these bundles are apparently normal, many atrophic, with the primitive fibrillæ lost and the appearance of an extension of the primitive bundles directly into the connective tissue of the scar. The idea is given of the existence and marked thickening of the sarcolemma sheath about the primitive bundles and of septa within the bundles separating the ultimate fibrils. The loss of muscle substance leaving these elements behind, apparently occasions the appearance of metaplasia just mentioned, in a passive way, however. Such apparent remnants stain as connective tissue with Mallory's special connective-tissue stain (not absolute, as formalin was used here as a fixative) and so, too, transverse sections of what seems to be atrophic primitive bundles stain in the sheath and in the interior in the same way. In the cicatricial tissue may also be seen remaining nuclei of former muscle bundles, sometimes in some state of disappearance as in solution, again intact and then often with a somewhat spindle-shaped mass of protoplasm about them, as if forming a large, young connective-tissue cell, staining with the special stain as connective tissue.

"No direct continuation of these cells into fibrillæ of connective tissue could be seen; there was no evidence of the multiplication of the nuclei of these bodies; numerous retrogressive forms and often isolated granules of polar pigment indicating the previous position of the nuclei were seen. For these reasons it is concluded that no real active part in regeneration into connective tissue of the scar is borne by these cell-like remnants. In other portions of the heart muscle the usual moderate interstitial fibrosis is seen. The muscle substance is in its degeneration near the scar, the seat of a liquefying process producing large vacuoles in its substance; and here and there finer vacuolation suggests the existence of fatty degeneration. The vessels are generally more or less fibrotic."

We feel that this case requires little comment. No one would hesitate to label it hysteria. The psychic picture is complete. The mental peculiarities, the motor phenomena, the vesical symptoms, the one form of therapeutic success are all characteristic.

Both Dercum's notes and our own comments dwell upon one striking feature, the fact that certain positions, passively caused or voluntarily produced, gave rise to definite extension of the spasms to the quieter arm and at times to the entire body.

This phenomenon is of great interest. Dr. Dercum speaks of it as like an overflow of nerve force, and it recalls to mind the explanation of the effects of reinforcement of knee-jerks given by Drs. M. J. Lewis and S. Weir Mitchell.

We are tempted to ask if restraint of the affected arm during a fit of Jacksonian epilepsy will be found to cause extension elsewhere of the limited convulsive motions. It seems probable that such restraint during a Jacksonian attack would have a tendency to cause extension of the convulsive movements to other parts of the body, because in epilepsy the muscular convulsion appears to act as a relieving release to excessive energy stored up in the cortex. Restraint of the spasms in epilepsy sometimes is followed by sensations that are more unpleasant than are the spasms. Thus Gowers remarks: "The arrest of the fit, by a ligature or a blister, sometimes causes so much giddiness and distress that some patients have considered the remedy worse than the disease."

In this present case the increase and spread of spasms by restraint of the primary spasm tempts to speculative hypothesis, but the physiologic mechanism is under no theory clear. If one

could dam up explosive nerve energy in its originative center until it overflows its normal nerve channels and sweeps over many neural centers and channels in disorderly discharge, this is conceivable. But when these outbursts are evoked by lifting a limb or restraining an habitual spasm at a distance from the center of effluent energy, the reason of the wide extension is not easy to explain; for in the case of a spasm forcibly checked we are only controlling the mere exhibition of disorderly muscular discharges and apparently not the primary outflow of nerve force.

This very interesting fact of restraint of spastic motion, causing remote or even general spasms, is not single in the experience of one of us.

Dr. Mitchell saw, in the Civil War, a soldier who had a see-saw spasm of the left foot, caused by a nerve wound of the sciatic. The flexors and extensors acted by turns, so as to keep the foot in constant motion. When it was held firmly the man was seized at once with a general left lateral convulsion, in which the face moved but slightly, without ocular spasms or loss of consciousness, but with occipital pain. As soon as the foot was released the other motion ceased. Sensibility was impaired from the peripheral lesion.

In the case of Col. P., described on page 364 of Dr. Mitchell's book on *Nerve Injuries*, there was a continual irregular threshing motion of the arm stump, which ceased for a time when the stump was exercised in voluntary motion, but which extended over a large region of the same side (right), with a sense of discomfort in the head if an attempt were made by another to restrain the spastic movements in the stump.

The purpose of this paper is to give the result of minute pathologic study of an uncomplicated and lasting case of undoubted hysteria.

The conclusions reached justify us in stating that with our present methods the most typical hysteria lasting for years presents no sign of representative organic lesion. This is, however, the wisdom of to-day; that of to-morrow may be based on other and more refined methods and be very different.

The case has other than this merely negative value. It raises

the question of why restraint causes generalized spasm. It suggests consideration of the share which even hysteric mental attributes may have in this sequence, and it illustrates how large and how lasting may be convulsive symptoms without their leaving a record on the long-disordered centers whence came this overflow of energy without sign of fatigue.

A CONTRIBUTION TO THE PATHOLOGY OF HYSTERIA BASED UPON AN EXPERIMENTAL STUDY OF A CASE OF HEMIANESTHESIA, WITH CLONIC CONVULSIVE ATTACKS SIMULATING JACKSONIAN EPILEPSY.

By MORTON PRINCE, M.D., and BORIS SIDIS, A.M., Ph.D.,

assisted by

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of Boston.

The following observations are offered as a contribution to the pathology of hysteria. The experimental results obtained confirm the modern theory of the disease and corroborate the various and numerous observations which have been made of recent years in France, Germany and this country. These researches have compelled us to recast our views of the pathology of hysteric phenomena, though a knowledge of this work has not yet found its way into the text-books. This is our reason for presenting this study before this Society.

The pathology as laid down in text-books may be exemplified by the following references:

Walton (Wood's *Handbook*) states: "Post-mortem investigation gives no clue to the morbid process and theoretic study of its nature has led as yet to little more than conjecture." . . . "Most of the paralytic symptoms, for example, are best explained on the supposition of decreased irritability of the cortical centers, while the spasmodic symptoms allow of explanation in part on the ground of their exalted irritability and in part on that of diminished inhibition."

Gowers, in discussing the pathology, states that "hemianesthesia must be ascribed to an inhibition of a sensory center relatively low," and that "this disturbance of lower centers has disclosed facts (!)

hitherto scarcely suspected and of much physiologic interest regarding this capacity for limited functional derangement." He then goes on to explain hemianesthesia by inhibition and infers a fanciful arrangement for its arrest, etc.

Sachs, although referring in a footnote to Breur and Freud's classic work which has helped to change our conception of the disease, contents himself with the opinion that "there is much room for theorizing, but there are very few facts to guide us," and that "the transfer of sensory disturbances from one-half of the body to the other would go to show that the two halves of the brain are evidently in sympathy with one another (to put it broadly) in this disease and that they can be alternately affected."

Dana attempts no theory.

Oppenheim makes a feeble reference to the psychic factors, but no attempt at explanation.

Lloyd (*Nervous Diseases by American Authors*) considers that "the pathology of hysteria is among the unsolved problems of the infant science of psychology."

Among the latest text-books Church and Peterson quote a few recent definitions, but practically do not consider the pathology.

Binswanger, in his extensive treatise on hysteria (Nothnagel's *Special Pathology and Therapeutics*), quotes the work of the modern French school, but apparently without comprehending it. He lays down the following metaphysic postulate, which seems to be absolutely devoid of meaning: "The hysteric alteration consists in a disturbance of the normal exchange between the psychic and the material processes. This occurs in two ways: on the one hand, the psychic process fails to be awakened parallel with a definite series of material cortical excitations, or are only incompletely aroused; on the other hand, correlated with a material excitement of the cortex, an excessive amount of psychic activity takes place, which excites every variety of reaction to the whole innervation process which arises in or is controlled by the cortex."

Strümpell thus reasons: "If the normal exertion and inhibition of the will-power be broken down, so that *unreasonable* will-stimuli are created and reach the muscles, we have hysteric convulsions, contractures or cramps. If there are present in the consciousness images of awaited or feared objects, and if these images be intensified by the conditions of the disease into *true subjective irritations* of consciousness, we shall have hysteric pains and neuralgias."

The following comment on this is fairly deserved:

"This piece of scientific speculation, as to its lucidity, reminds one of the definition of love given by a Platonist: 'Love is the ideality of reality of a part of the totality of the Infinite Being.'"

All these earlier speculations are not only trivial, but are now known to be erroneous, for recent researches have thrown a great deal of light upon the pathology of the disease, although much remains to be done to give a complete understanding of it.

The study of the case here reported is of clinical interest in that:

1. It confirms the work of previous observers in regard to the nature of hysteric anesthesia; that is to say, the anesthesia is not due to inhibition of sensory centers or any kind of suppression of their activity; in fact, it is not true anesthesia at all, but is due to a dissociation of consciousness, probably corresponding to a functional dissociation of systems of cortical neurons.

2. It shows the purely functional character of the epileptiform attacks and their origin in dissociated psychic states.

3. It emphasizes the importance of understanding the pathology of the attacks in order to effect a cure.

History. Mr. M., aged twenty-one years, was born in Russia and came to this country four years ago. His family history as far as can be ascertained is good. There is no nervous trouble of any sort in the immediate or remote members of his family. The patient himself has always enjoyed good health. He is a very intelligent young man of good habits. He does not use alcohol or tobacco and gives no venereal history.

He was kindly referred to us by Dr. K. M. Davidson, of Boston, for epileptiform attacks and anesthesia of the right half of his body. The attack is preceded by an aura consisting of headache and a general feeling of malaise. The aura lasts a few days and terminates in the attack, which always sets in about midnight, but *when the patient is fully awake.* The attack consists of a series of spasms rhythmic in character and lasting about one or two minutes. After an interval of not more than thirty seconds the spasms set in again. This condition continues uninterruptedly for a period of five or six days (a sort of status epilepticus), persisting during the time the patient is awake and ceasing only during the short intervals or rather moments of sleep. Throughout the whole period of the attacks the patient is troubled with insomnia. He sleeps restlessly for only ten or fifteen minutes at a time. On one occasion he was observed to be in a state of delirium as found in postepileptic insanity and the so-called 'Dämmerzustande" of epilepsy. This delirium was observed but once in the course of five years. The regular attack is not accompanied by any delirious states or "Dämmerzustande." On the contrary, during the whole course of

the attack the patient's *mind remains perfectly clear*. He does not lose consciousness even for a moment, and not the least trace of emotional disturbance, such as fear, for instance, can be found. During the period of the attack the whole right side becomes anesthetic to all forms of sensations, kinesthesia included, so that he is not even aware of the spasms unless he actually observes the affected limbs. Otherwise he remains unconcerned, perfectly *placid* and unruffled as if nothing special is happening to him.

The affected limbs, previously normal, also become paretic. After the attack has subsided the paresis and anesthesia persist (as sometimes happens in true idiopathic epilepsy) for a few days, after which the patient's condition remains normal until the next attack. After his last attack, however, the anesthesia and paresis continued for about three weeks.

The first attack occurred five years ago, since which time up to this last year he has had every year one attack which, very curiously, sets in about the same time, namely, about the month of January or February. During the last year, however, the attacks have increased in frequency, so that the patient has had four at intervals of about three or four months. On two different occasions he was in the Boston City Hospital for the attacks.

Examination. Examination of the patient made three weeks after the last attack showed the following: Pupils are equal and react promptly to light and accommodation. Knee-jerks slightly exaggerated. No ankle clonus. No Babinsky. There was a profound right hemianesthesia, including the right half of the tongue, with a marked hypoesthesia of the right side of the pharynx. All the senses of the right side were involved. The field of vision of the right eye was very much limited. The ticking of a watch could not be heard more than three inches away from the right ear. (Hearing in left normal.) Taste and smell were likewise involved on the right side. The muscular and kinesthetic sensations on the right side were very much impaired.

The patient's mental condition was good. He was well balanced and did not give evidence of any emotional disturbances. He states that he has few dreams, and those are insignificant, concerned as they are with the ordinary matters of his daily life. Occasionally he dreams that he is falling, but there is no definite content to the dream.

These findings were indicative of functional rather than organic disease. The *previous history* of the case was significant. The first attack came on after peculiar circumstances, five years ago, when the patient was sixteen years of age and living in Russia. After returning from a ball one night he was sent back to look for a ring which the lady whom he escorted had lost on the way. It was after midnight and his way lay on a lonely road which led by a cemetery. When near the cemetery he was suddenly overcome by a great fright, thinking that somebody was running after him. He fell and lost consciousness. By the time he was brought home he had regained consciousness, but there existed a spasmodic shaking of the right side, involving the arm, leg and head. The spasm

persisted for one week, during which time he could not voluntarily move his right arm or leg, and the right half of his body felt numb. There was also apparently a loss of muscular sense, for he states that he was unaware of the shaking of his arm or leg unless he looked and saw the movements. In other words, there was right hemiplegia, anesthesia and spasms. For one week after the cessation of the spasms his right arm and leg remained weak, but he was soon able to resume his work and he felt as well as ever. Since then every year, as already stated, *about the same month* the patient has an attack similar in every respect to the original attack, with the only exception that there is no loss of consciousness. Otherwise the subsequent yearly attacks are photographic pictures, close repetitions of the original attack.

This history, obtained from himself the patient and his family, was still further suggestive, though not a proof, of the functional character of the attacks. Furthermore, even though functional, nothing was evident to show the deeper pathology of the affection; that is to say, the exciting and underlying cause of the attacks and the anesthesia.

A series of experiments accordingly was undertaken for this purpose: First, as to the *anesthesia*. If the anesthesia was hysteric, as is now well known, sensory impressions ought to be felt even though the patient was unconscious of them, and we ought to be able to get sensory reactions of a well-known sort.

Tests Showing the Functional Nature of the Anesthesia: Visual Hallucinations. The experiments which were made to determine the nature of the anesthesia produced interesting results. These experiments are of a well-known class which have been frequently made use of to show that the anesthesia is not a true anesthesia, but that impressions from the anesthetic parts which seem not to be felt are really perceived subconsciously.

They may be made in several different ways. The method we made use of consisted in producing a visual hallucination whenever the anesthetic hand was touched. That is to say, if the anesthesia is functional, although the subject does not consciously perceive the tactile impressions, he sees the image of a number which corresponds with the number of times the hand is pricked or touched. This was found to be the result in this case. Whenever the hand was pricked a certain number of times successively, he always saw that number as an hallucination. The number was always correct and showed that subconsciously the pricks must have been felt.

The details of the experiment were as follows: The anesthetic hand was placed behind a screen and the patient was told to look in a glass of water and tell what he saw there. Impressions made on the anesthetic hand gave rise to visual hallucinations symbolically representing the sensory stimuli. Thus, for example, when his hand was touched, very lightly, five times, he saw the figure 5 very vividly and described it in detail. He saw the number written; it looked very large, and he saw it written on the back of a hand.

The intensity of the hallucination was well brought out when, projecting the

hallucinatory hand on a screen instead of in the water, the patient outlined it with a pencil. When one of us placed his hand on the screen by the side of the hallucinatory hand, and the patient was asked to tell which hand looked more real, he insisted that both hands looked equally real, except that the hallucinatory hand looked a little farther away.

Other tests also showed that the *subconscious* reactions to impressions from the anesthetic hand were more acute than the conscious reactions to impressions from the normal hand. So we have the so-called "psychopathic paradox" that "the *functional anesthesia is a hyperesthesia.*" (Sidis.)

It is perfectly evident, then, that there could be no inhibition of the sensory centers, or suppression of their activity, or whatever else it may be called. In spite of the apparent profound anesthesia the pinpricks were felt and perceived. The perception of them gave rise to hallucinations of a character that showed the pinpricks were counted and localized in the hand. The result of these tests is in accord with previous observations which have demonstrated that in hysterics all sensory impressions received from anesthetic parts, while they do not reach the *personal* consciousness, are, as it is called, subconsciously perceived. The accepted interpretation of such phenomena is this: Inasmuch as the sensations are perceived, the failure of the subject to be conscious of them must be due to a *failure in association.* The perception of the sensation is *dissociated* from the personal consciousness. More than this, these dissociated sensations are capable of a certain amount of independent functioning; hence the hallucinations and also the well-known failure of hysterics to be incommoded by their anesthesia. This condition of dissociation is now recognized as that underlying hysteric anesthesia.

Study of the Attacks. For the purpose of studying the attacks themselves the patient was hypnotized. He went into a deep somnambulic condition in which, however, the *anesthesia still persisted.* This showed that the dissociation of the sensory impressions was unchanged. In hypnosis he related again the history of the onset of the trouble. But now his memory became broader and he was able to give the additional information, which he could not do in his waking state, that at the time he was frightened he fell on his right side. Moreover, he recalls what he does not remember when awake, that throughout the period of his attacks when he falls asleep he has very vivid dreams of an intense hallucinatory character, all relating to the fright and fall of five years ago. In these dreams he lives over and over again the experience which was the beginning of his trouble. He again finds himself in his little native town, on a lonely road; he thinks someone is running after him; he becomes frightened, calls for help, falls, and then wakes up with a start, and the whole dream is forgotten. After he wakes he knows nothing of all this; there is no more fear or any emotional disturbance; he is then simply distressed by the spasms.

Subconscious Reproduction of the Attacks. While testing the anesthesia during hypnosis an attack developed; his right arm and leg began to shake, first

mildly and then with increasing intensity and frequency. His head also spasmodically turned to the right side. The movements soon became rhythmic. Arm and leg were abducted and adducted in a slow, rhythmic way, at the rate of about thirty-six times per minute. With the same rate and rhythm the head turned to the right side with chin pointing upward. The right face was distorted by spasm, as in great pain. The left face was unaffected. Pressure over his right side (presumably where he struck when he fell) elicited evidences of great pain. Respiration became deep and labored and was synchronous with each spasm. The whole simulated Jacksonian epilepsy. It is noteworthy that the knee-jerk on the right side was exaggerated by comparison with the left during the attack. Consciousness persisted unimpaired, but showed a curious and unexpected alteration. When asked what was the matter he replied, to our surprise in his native dialect (a German dialect), "I do not understand what you say." It was found that he had lost all understanding of English, so that it was necessary to speak to him in German. His answers to our questions made it apparent that during the attack, as in his dreams, he was living through the experience of five years ago, which had originally excited his trouble. The attack was plainly an hallucinatory one. He said that it was now 1898, that he was sixteen years old, that he was in Rovno (Russia), that he had just fallen because he was frightened, that he was lying on the roadside near the cemetery, and that he wanted somebody to pick him up. The hallucinatory state developed farther, the patient living through, as in a dream, the whole experiences that had taken place at that period. Now he was in a carriage, though he did not know who put him there. Then in a few moments was again home, in his house, with his parents attending on him as in the onset of his first epileptiform seizures. The attack terminated at this point and thereupon he became perfectly passive and when spoken to answered again in English. Now he was again twenty-one years old, was conscious of where he was, and was in absolute ignorance of what had just taken place.

Disappearance of the Anesthesia and Automatic Reproduction of the Attacks. It was found that an attack could regularly and artificially be induced if the patient in hypnosis was taken back by suggestion to the period when the accident happened.

The experiment was now tried of taking him back to a period antedating the first attack. He was told that he was fifteen years old, that is, a year before the accident occurred. Now again he could no longer speak or understand English; he was again in Rovno, engaged as a salesman in a little store, had never been in America and did not know who we were. But testing sensation it was found that it had spontaneously returned to the hand. *There was not a trace of the anesthesia left.* The hand which did not feel deep pinpricks before now reacted to the slightest stimulation. *Spontaneous synthesis of the dissociated sensory impressions had occurred.* Just as formerly before the accident sensation was in normal association with the rest of his mental processes, so now this association

was re-established with the memories of that period to which the patient was artificially reduced.

The patient was now (while still believing himself to be fifteen years old) taken a year forward to the day on which the accident happened. He says he is going to the ball to-night. He is now at the ball; he returns home; he is sent back to look for a ring. Like a magic formula it calls forth an attack in which again he lives through the accident—the fright and the spasms. With the onset of the spasm dissociation again occurs, the *hand becomes anesthetic* and remains anesthetic after the subject is awakened.

It was thus possible to reproduce an attack at any time with clock-like precision by taking him back to the period of the accident and reproducing by an hallucination all its details. Each time the fright and the physical manifestations of the attack (spasms, paresis and anesthesia) developed. These induced attacks were identical with the spontaneous attacks, one of which we had occasion to observe later.

Relation to Various Forms of Neuroses. This case is similar to those of this sort which had been studied by Janet in France, Breuer and Freud in Germany, and a number of cases studied in this country by Sidis and Prince.

The question is further raised by such cases as this, whether some of those cases of fear neurosis studied by one of us (Prince), in which there are manifested all the physical manifestations of fear, without the presence of the emotion itself—thus presenting a psychic paradox—whether some of these cases have not as a foundation a subconscious and unrecognized fear.

Pathology. This analysis enables us to understand to a large extent the pathology of the attacks. At the time of the accident the intense emotional disturbance, the fright, acted as a dissociating agent, and dissociated the sensory and motor images of one-half of the body in such a way that they were no longer *en rapport* with the personal consciousness. These dissociated elements were not, however, inhibited or incapable of functioning, as is shown by the hallucinations and other phenomena brought out in the test experiments. In cases of this kind the dissociated sensory and motor images become what is called "subconscious" and capable of automatic activity.

Sensory impressions are subconsciously perceived, and motor images subconsciously excited. The dissociation (through the influence of the emotion) of these sensory and motor images and their automatic subconscious excitation *is* the attack. The original

emotion, fear, remains (unknown to the subject) dissociated in the subconsciousness as a fixed state. Here from time to time it acquires a separate and independent activity. At periodic intervals, as under the stress of some emotion, or by association of ideas, its dormant activity is awakened, and, though still unknown to the patient, gives rise to the same sensory-motor disturbances which characterized the original experience. These subconscious, dissociated states are so much more intense in their manifestations because of being cut off, by the very fact of their dissociation, from the inhibitory influences of the normal mental life.

The pathology of such cases as this and of hysteria in general, then, consists on the one hand in the dissociation of the mental (and cerebral) processes and on the other in the independent and automatic activity of the disaggregated psychic (and cerebral) states. Dissociation and automatism are the two fundamental processes.

The case, furthermore, gives an insight into the nature of many of the cases of "traumatic neuroses," of "psychic" epilepsy, of hysteroepileptic seizures, and of some forms of insistent ideas and impulses.

TREATMENT (*Reassociation*). Once a case of this kind has been analyzed and its pathology determined, it is possible to bring about a cure by synthesizing the dissociated mental states with the waking consciousness; or, in popular language, by making the mind whole once more. For this purpose the dissociated lost memories are brought into full light of the waking consciousness, which is thus made to have a complete knowledge of them. So long as normal associations are maintained between the *lost memories* (or mental states) and the normal mental life, the system which before was dissociated can no longer be thrown into independent activity, and the train of symptoms to which that activity gave rise can no longer appear.

That is what we did in this case. In hypnosis he was made to realize that he was twenty-one years old, he was given a knowledge of his present life, of the subconscious states with their attacks, and was made to realize the absurdity of his really being sixteen years old. In his waking life he was made to remember all the events of the incident. The subconscious and the waking memories were thus united. During the whole course of treatment by association, a course which covered a period of several weeks, the dissociated system was coming to the surface of consciousness more frequently

and in a fuller and more developed form. The attacks were more frequent, but of shorter and shorter duration, lasting but a few hours instead of several days. Finally, the system became stable and permanently associated.

After the stability of association was effected it was found that he could no longer be made to pass into that particular hypnotic state. The subconscious fear could no longer be excited, the attacks could no longer be artificially induced; indeed, the anesthesia and the spasms could no longer be developed.

Although there is no reason to suppose that he is not cured (for a complete proof of a cure a year or more must pass), still, as the attacks cannot be artificially induced, it is not probable that they can be excited by the associations which usually call them forth.

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DISCUSSION.

DR. PUTNAM: I was very much interested in Dr. Mitchell's case, which is sure to carry great weight. I think it may be said, however, that there is no positive reason why we should expect to find pathologic changes in the central nervous system in consequence of the long continuance of muscular action, even of this degree. In "athetosis" and in the case of the heart's action, we have examples of almost constant movement not leading to destructive changes, but rather to the reverse condition. It is a question rather of fatigue than of motion, and fatigue is proportionate to "attention" rather than to muscular action. Therefore degenerative changes would be expected rather in the "occupation neuroses" than in the relatively automatic movements of hysteria.

As regards Dr. Prince's paper, I am glad the subject of which he speaks has been brought up, for it introduces us to a field of research which has been worked by certain observers, but which has been rarely referred to in a general meeting of this sort. I saw the patient whose case Dr. Prince has described, and the performances were striking indeed.

DR. MITCHELL: I would say but a word in regard to one thing that Dr. Putnam said. I think we might expect to find some marked pathologic evidence

from such long-continued muscular actions. Dr. Putnam will recall the paper of Dr. Hodges on the obvious effects of fatigue on the nerve cells, and it seems to me quite natural to look for similar and lasting results from the constant movements of this patient for so many years.

DR. WOOD: It seems to me that in order to account for this thing you have simply got to suppose that the nerve centers of organic life take on some of the functions of centers of inorganic life. The heart moves constantly for many years, but leaves on its ganglia no record of its contractions. I have long believed that these movements of the hysteric are like the involuntary movements of inorganic life, and perhaps it is not the movement, after all, that leaves the record upon the nerve cell, but the volitional impulse.

It seems to me probable that when a nerve cell responds to what may be called its natural impulse this response is not accompanied by fatigue; but that when a volitional impulse reaches it from the brain the translation of this impulse into muscular action produces fatigue.

EXPERIMENTAL ARTHRITIS AND ENDOCARDITIS PRODUCED BY A STREPTOCOCCUS ISOLATED FROM THE BLOOD OF A CASE OF RHEUMATISM, ENDOCARDITIS AND CHOREA.

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ALTHOUGH rheumatic fever is believed by many to be an acute infectious disease, the specific agent concerned in its causation has been widely disputed, and even at present few authorities are agreed as to its etiology. The symptomatology, the frequent association with endocarditis and the unique character of the disease have always suggested that rheumatic fever was due to some bacterial infection, and, therefore, it is not surprising that most of the investigations regarding its etiology should be carried out with this thought in mind. The results of many of the earlier studies were confusing and often contradictory, but certain recent investigations, coming especially from Germany and England, seem to throw some light upon the problem.

The intimate relationship between chorea and rheumatism[1] and the artificial production of chorea by intravenous inoculation of a diplococcus from a case of rheumatism, as claimed by Beattie, to be referred to later, make this subject doubly interesting.

[1] Lewis, Seasonal Relations of Chorea and Rheumatism, American Journal of the Medical Sciences, September, 1892.

In much of the earlier work done by Sahli,[1] Singer[2] and others, cultures from the blood, urine and joint fluid of cases of rheumatic fever frequently yielded not one but several types of bacteria. Among these, staphylococci, streptococci and even certain bacilli belonging to the colon group were described. Experimental inoculations proved the virulence of these bacteria, but arthritis and endocardits could scarcely, if ever, be reproduced. Contradicting these observations were the results reported by Chvostek,[3] and Kraus,[4] who could not obtain any growth of bacteria in cultures from the blood, joint fluid or urine. In 1897 Achalme[5] published an account of his work with a spore-bearing anaërobic bacillus which he had previously described in 1891. This organism was cultivated from the blood of cases dying of acute articular rheumatism. The bacillus grew best in milk. Inoculations into animals produced spreading hemorrhagic phlegmons and general septicemia. The later work of Menzer and others goes to show, however, that this organism may be obtained from the bodies of cadavers, or even from milk which is not overcarefully sterilized, the spores being very resistant to heat. Walker considers that this organism is bacillus enteritidis sporogenes.

Wassermann,[6] in 1899, described a diplococcus or streptococcus which he obtained in cultures from the heart's blood and endocardial vegetations of a child dead of rheumatism, endocarditis and chorea. This diplococcus developed in the ordinary culture media exactly like streptococcus pyogenes, but produced the most remarkable lesions in animals. A series of successive intravenous inoculations into eighty rabbits showed that it was possible to set up a multiple arthritis which rarely proved fatal. The joint symptoms occurred with great regularity, and developed only after an incubation period of three to six days. Frequently the infection spread from one joint to another. Soon these results

[1] Deuts. Arch. f. klin. Med., 1892, Bd. li. p. 451.

[2] Aet. u. Klinik des akuten Gelenkrheumatismus, 1898, Leipzig, Verhandl. des XIX. Cong. f. inner Med., 1901, p. 441; Wien. klin. Woch., 1901, No. 20.

[3] Wien. klin. Wochen., 1895, No. 26, p. 469.

[4] Zeit. f. Heilkunde, 1896, Bd. xvii.

[5] Annal. de l'Inst. Pasteur, 1897, p. 845; Gaz. med. de Paris, 1901, No. 14, p. 105.

[6] Berl. klin. Wochen., 1899, No. 29, p. 638.

were confirmed by Triboulet,[1] in France, who was able to produce in some of his rabbits endocarditis, pericarditis and pleurisy. Later, Menzer[2] and Meyer[3] obtained streptococci from the throats of patients suffering from rheumatic angina. These organisms were characterized principally by their power of producing multiple arthritis in rabbits. The joint lesions occurred constantly, and were often associated with a vegetative endocarditis. Singer[4] somewhat later announced that the streptococcus which he had previously described was identical with the organism obtained by these observers.

In England the extremely severe type of rheumatic fever has afforded an excellent field for the study of this disease, and the results obtained by English observers have, perhaps, been more striking than those reported from other countries. Poynton and Paine,[5] since their first publication, in 1900, have isolated a diplostreptococcus from twenty-two cases of rheumatic fever. The organism was obtained occasionally from the blood before death in severe cases, but usually from the blood, endocardial vegetations and complicating lesions after death. Intravenous inoculation into rabbits was followed by an interesting train of lesions. Monoarthritis and polyarthritis was an almost constant result, while endocarditis, pericarditis and pleurisy were occasionally encountered. The organism could be cultivated from the joints and endocardial growths of the animals. Among other lesions subcutaneous fibroid nodules were described in which the particular diplococcus could be demonstrated. Definite chorea could never be reproduced in any of the animals. Poynton and Paine consider that this organism is identical with that described by Wassermann and Triboulet, and believe that it is the specific cause of rheumatic fever. Recently Ainley Walker[6] and Walker

[1] Compt.-rend. de la Soc. de Biolog., 1898, Bd. v. p. 124; Gaz. des hôp. des Paris, 1902, tome lxxv. p. 1439; ibid., 1903, tome, lxxvi. p. 405.

[2] Etiology des akuten Gelenkrheumatismus, Berlin, 1902.

[3] Zeit. f. klin. Med., 1903, Bd. xlvi. p. 311; Verh. des XIX. Cong. f. inn. Med. 1901, p. 452; Verh. des Vereins f. inn. Med., January 7, 1901.

[4] Loc. cit.

[5] Lancet, 1900, vol. ii. p. 861; British Medical Journal, 1901, vol. ii. p. 779; Medical Press and Circular, 1903, vol. cxxvi. p. 478

[6] Practitioner, 1903, vol. lxx. p. 185.

and Beaton[1] have fully confirmed Ponyton and Paine's results. They were able to cultivate a diplococcus from fifteen cases, including acute rheumatism, rheumatic endocarditis, pericarditis, chorea and endocarditis. Intravenous inoculations into animals produced monoarthritis and polyarthritis, pericarditis, endocarditis, septicemia and death. Beattie[2] claims to have produced chorea as well as endocarditis and arthitis in rabbits inoculated intravenously with a diplococcus obtained at autopsy from the knee-joint of a case of rheumatic fever. Finally, Shaw[3] has made a comparative study of the cocci isolated by Wassermann, Ponyton and Paine and Walker. He finds that these various bacteria produce practically the same effects when inoculated into rabbits and monkeys, and may give rise to endocarditis, pericarditis, myocarditis, arthritis, pleurisy and iritis.

In America almost no work had been done on this subject. Dana,[4] in 1894, found diplococci in sections of the meninges of a child dead of chorea, but since cultures were not made the character of this organism must remain in doubt.

The recent papers of Poynton and Paine, Walker, and Menzer deal quite extensively with the literature upon the subject. In view of the interesting experiments which have been made in England and Germany it was thought advisable to record the following case of rheumatism, endocarditis and chorea:

M. H., female, aged eight years, admitted into Orthopedic Hospital and Infirmary on October 15, 1903, under the care of one of the writers, with the following history furnished by Dr. W. T. Skinner, of Glasgow, Delaware:

"Toward the latter part of August or early part of September, 1903, the child was taken sick; she had fever and was confined to bed with a swollen and painful ankle. Under salicylate of soda the child rapidly improved, and was able to run about and play. Although she had relief from pain and swelling, she did not appear to be well and was languid. She was given quinine in tonic doses and was not seen again until toward the end of September, when she began to exhibit choreic movements, which were particularly noticeable in her hands, feet and face and not unilateral; she also now complained of stiffness and soreness of the wrists. Three days later, September 29th, the

[1] British Medical Journal, 1903, vol. i. p. 237; ibid., vol. ii. p. 659.
[2] Journal of Pathology and Bacteriology, 1904, vol. ix. p. 272.
[3] Ibid., 1903, vol. ix. p. 158.
[4] American Journal of the Medical Sciences, 1894, vol. cvii. p. 31.

movements had become so severe that the child could not swallow, and the sides of the bed had to be padded to prevent her injuring herself in her violent movements."

This condition continued until brought to the Infirmary on October 15th.

Upon admission, at 5 P. M., after a journey from Delaware, the child was perfectly limp and with but very slight choreic movements. She was unable to voluntarily move hand or foot and the limbs hung as if paralyzed. She could not speak and scarcely even swallow. The temperature was not taken, but the child seemed entirely apyretic. No heart murmurs could be detected. Pulse and respiration were both very rapid and the latter shallow. On the morning of the 16th her temperature suddenly rose to 107°, and the choreic movements were excessive and so violent as to necessitate the padding of the sides of the crib. Her respirations were 76 per minute, and her pulse was 138.

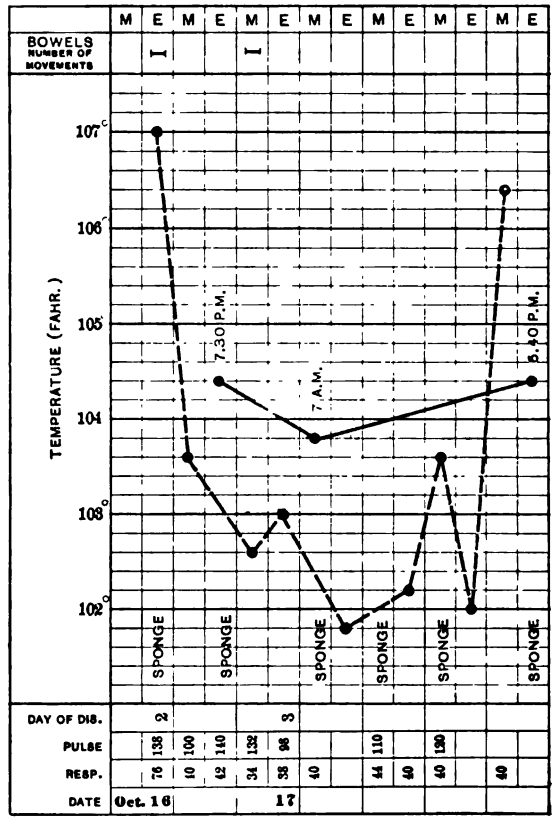
Under sponging and chloral by mouth and rectum the temperature rapidly fell, becoming 101° by the morning of the 17th; the movements still, however, remained severe. Arsenic was first administered by the mouth and later hypodermically. No cardiac murmurs could be heard on the 16th, although they were carefully sought for, but on the morning of the 17th a soft apex systolic murmur was detected, which rapidly increased in intensity until her death, on the evening of the 17th, with a second rise of temperature to 106.5°. A blood culture was made on the afternoon of the day of her death. Although the greatest care was taken, the constant agitation was beginning to cause abrasions of elbows, shoulder-blades, hips and heels. No examination of the urine was made, as none could be collected without catheterization, owing to the violent movements. No autopsy was allowed.

The accompanying chart shows the course of the fever.

Cultures were made from the median basilic vein about twelve hours before death. Three ounces of blood were drawn, with aseptic precautions, and put into two flasks, one containing about 250 c.c. of litmus milk and the other about 250 c.c. of bouillon, to which 10 c.c. of hydrocele fluid had previously been added. After forty-eight hours the milk flask showed a marked acid reaction. The bouillon flask did not show any growths. Cover-slips from the milk flask revealed a small delicate diplococcus which occasionally formed chains of short length. The organism was immediately plated.

In agar plates both surface and deep colonies were exactly like those of streptococcus pyogenes. The morphology of the organism was that of a delicate diplococcus growing often in long chains in fluid media. Gram's stain was held, provided the decolorization in alcohol did not last more than two to three minutes. On plain agar slants the growth was exceedingly delicate and sparse. Separate tiny gray pinpoint colonies were scattered over the surface. On hydrocele agar the growth was somewhat more luxuriant, while the condensation water showed marked clouding. On plain agar the cultures died within a week or ten days, but on hydrocele agar slants they could readily

be kept alive for two to three weeks. This medium was, therefore, used entirely for the transplantation of the stock cultures. Milk was rapidly acidified and often clotted after a week's growth. In bouillon there was a scant growth collected in minute granules at the bottom of the tube. If, however, the reaction was somewhat alkaline (—10 Eyre), the growth was heavier. A growth could always be obtained in gelatin. There was no liquefaction.



On October 22d, five days after the organism had been isolated, two rabbits were inoculated intravenously with suspensions made with bouillon from a twenty-four hours' growth on two hydrocele agar slants. Rabbit I. received 2 c.c. Rabbit II. received 1 c.c. On October 25th, three days after inoculation, both rabbits seemed well.

26th. Rabbit I. lies quite still and seems sick. When disturbed it moves about with difficulty and appears to drag right hind leg.

November 11th. Rabbit I. has remained definitely lame in left hind leg. Left ankle-joint is swollen. Hops about with a good deal of difficulty. Rabbit II. has also been quite lame in hind legs, but has apparently recovered and now hops about with moderate ease. Rabbit I. killed. At autopsy 30 c.c. of cloudy port-wine colored fluid was found in the peritoneal cavity. Both pleural cavities contained clear, straw-colored fluid. The spleen was rather large. The liver, kidneys and lungs appeared normal. The heart was large and distended with blood. The walls were thin and cavities dilated. The muscle was quite soft, friable, pale and mottled with yellow patches. All the valves appeared normal.

The right ankle was about the size of a large cherry. The surrounding tissues were not involved. When the joint was opened a thick, pultaceous, creamy fluid escaped, but was mixed with some cloudy glutinous fluid. The left knee was slightly swollen, and when incised a moderate amount of thick, semitranslucent, glutinous fluid escaped. The left ankle was much like the right, except that the joint was not so much swollen. All the other joints appeared normal.

Cover-slips from the affected joints showed a few leukocytes, stringy mucoid material, phagocytic epithelioid cells and many diplococci usually within leukocytes. The diplococci stained well in gentian violet, and were not decolorized by Gram's method. Cultures were made on hydrocele agar from heart's blood, liver, spleen, kidney, peritoneal cavity, right and left ankle and right and left knee. None of the cultures showed any growth except those from the right and left ankles. From these two situations a meagre but pure growth of streptococci was obtained. The organism on subcultures agreed in every respect with the streptococcus previously described.

A third rabbit was inoculated with the organism obtained from the right ankle of Rabbit I. Three c.c. of a suspension of twenty-four hours' hydrocele agar culture in bouillon were injected into the ear vein. For three or four days the animal appeared perfectly well. After this time he gradually became lame in the hind legs and eight days after inoculation the left knee appeared definitely swollen. This was followed by involvement of the right ankle and later by slight swelling of the joints of forelegs. The animal rapidly grew much worse and finally died eleven days after inoculation. At autopsy extensive friable vegetations were found upon the mitral valve; there was an enlargement of the spleen, with anemic infarctions of both that organ and the kidneys. Both ankles were greatly swollen and contained pultaceous material and sticky, glutinous fluid. There was a varying amount of involvement of the right knee and hip, left knee, right wrist, elbow and shoulder, left shoulder and left wrist. A delicate diplococcus was found in cover-slips from the mitral vegetations in enormous numbers and from the heart's blood and all the affected joints. The organism was grown from the heart's blood, mitral vegetations, spleen, liver, kidney, right ankle, knee, wrist and elbow and left wrist. It proved

to be a streptococcus identical with the one obtained from Rabbit I. and from the original blood culture.

A fourth rabbit was inoculated in the same way as the others, with 2 c.c. of culture. About six days after inoculation the primary symptoms of lameness and difficulty in movements developed. Although the rabbit rapidly grew very lame and appeared quite ill, no definite swelling of the joints could be made out. The animal died nine days after inoculation. At autopsy practically every joint in the body showed some swelling and contained a moderate amount of thick, glutinous fluid. None of the joints were greatly increased in size, but some showed much more swelling than others.

Cover-slips from the right and left ankles, right shoulder, right and left elbow and left wrist showed varying numbers of polymorphonuclear leukocytes and epithelial cells, but always quantities of diplococci, usually within cells. Cultures were made on hydrocele agar from the heart's blood, right and left ankle and left wrist and on plain agar slants from the liver. Colonies developed only on the tubes from the joints. The cultures from heart's blood, spleen and liver showed no growth.

Finally, a fifth rabbit was inoculated intravenously in exactly the same manner as the others, with 1 c.c. of a twenty-four hours' hydrocele agar culture. The rabbit did not appear definitely ill for nine days, but by this time it was hopping about with difficulty, seemed ill and preferred to crouch in a corner of the cage. On December 12th the animal appeared generally in better condition, but was still lame and definite swelling of the left ankle-joint could be made out. After twenty-five days both ankles had become swollen, though the animal seemed generally better. The animal was killed on the twenty-fifth day after inoculation.

The peritoneal, pleural and pericardial cavities were normal. The heart, spleen, liver and kidneys did not show any marked pathologic change. On the right ankle the Achilles bursa was found to be swollen to about the size of a cherry, while there was slight increase in the size of the ankle itself. The left ankle was very extensively swollen. All the joints were normal except the right wrist. Although this joint itself was not swollen, over one of the extensor tendons there was a firm, rounded nodule about the size of a grape seed. On section a minute central soft point was seen. Cover-slips from this soft material showed a few leukocytes and epithelial cells, while here and there diplococci were occasionally found.

The organism was only recovered from the right ankle-joint.

A microscopic study of the organs from the four rabbits revealed the following conditions:

The heart muscle showed moderate grades of fatty degeneration, with swelling and parenchymatous degeneration of muscle fibres. In Rabbit III., which died of acute endocarditis, there were accumulations of small round cells and areas of polymorphonuclear leukocytic infiltration.

In one case there were areas of focal necroses in the liver. In the spleen and kidney of Rabbit III. definite anemic infarctions were seen, while in the latter organ many of the small vessels and glomerular capillaries were plugged with masses of diplococci.

The synovial membrane from the joints, showing various degrees of involvement, presented marked pathologic alterations.

In the earlier stages there were extreme edema, congestion, and slight infiltration of polymorphonuclear leukocytes and small round cells. In the latter stages the cellular infiltration was more intense and the fixed connective cells showed active proliferation. Epithelioid cells and small round cells were very numerous. The surface of the membrane was covered with polymorphonuclear leukocytes and granular debris. In one section many of the vessels of the synovial membrane were completely occluded by thrombi composed of fibrin, red blood corpuscles and leukocytes.

Great numbers of diplococci could readily be demonstrated in sections stained by the Weigert-Gram method.

To sum up, we have a streptococcus isolated before death from the blood of a case of chorea, endocarditis and rheumatism. This streptococcus is moderately virulent for rabbits when injected intravenously and gives rise with the greatest constancy to a multiple arthritis which is rarely fatal, unless, as in one case, it is complicated by an acute vegetative endocarditis. The onset of the joint symptoms is only noticeable after a more or less definite incubation period of four to nine days. Before this time the animals appear perfectly well. The joint involvement usually starts with swelling and tenderness in the ankles. Probably there is pain, too, for the rabbits move but little and limp when made to hop about. The infection may remain localized or spread to practically all the joints in the body. Small swellings may also develop upon the muscle tendons. The streptococcus can be recovered with great regularity from all the affected joints.

The organism, from its morphologic and biologic properties, could not with any certainty be differentiated from the usual varieties of streptococcus pyogenes.

Walker has emphasized the fact that the "micrococcus rheumaticus" grows readily in filtered cultures of streptococci from sources other than rheumatic fever. Marmorek believes that by this procedure various closely allied species of bacteria may be separated.

We found that the particular streptococcus under observation

grew fairly well in filtered twenty-four hours' bouillon cultures of streptococci from several sources, but occasionally it happened that streptococci from the blood of puerperal septicemia or other sources gave the same result. This particular biologic test was, therefore, thought unreliable. The interesting fact was pointed out by Walker[1] that the micrococcus rheumaticus when grown in alkaline bouillon is capable of producing large quantities of formic acid, whereas other streptococci form very small amounts of this acid. In this connection the same author has found that formic acid is present in the urine of patients suffering from rheumatic fever. When our organism was grown in bouillon (—10 Eyre) for six to eight days, and subsequently distilled with sulphuric acid, formic acid could be demonstrated in the distillate.

But in spite of these minor variations the fundamental resemblance culturally is very close between streptococci isolated from the blood or lesions of rheumatic fever patients and streptococci from other sources. On the other hand, the results of animal experiments seem to bring out possible differences.

The streptococci that have so far been described in rheumatic fever show a remarkably constant and uniform predilection for the joints, heart valves and serous membranes of the animals into which they are injected. Wassermann[2] produced joint lesions in eighty consecutive rabbits. Meyer[3] has found fungating and vegetative endocarditis in a surprisingly large number of animals after intravenous inoculation of streptococci obtained from the throat in rheumatic angina, while Poynton and Paine,[4] as well as Ainley Walker,[5] have observed monoarthritis and polyarthritis, endocarditis, pericarditis and pleurisy in their animals. In our own cases the mode of onset, the joint lesions themselves and the endocarditis were most striking. In every instance the lesions show such little variation and are so constant that they must attract attention. It is also worthy of note that, though the organism be passed through several animals, the virulence is little altered.

Experiments regarding the pathogenicity for animals of streptococci from sources other than rheumatic fever are not very numer-

[1] Loc. cit. [2] Loc. cit. [3] Loc. cit.
[4] Loc. cit. [5] Loc. cit.

ous. This portion of the question we were, unfortunately unable to investigate, owing to the difficulty in securing the large number of rabbits which would be necessary for such work. Meyer found that with attenuated cultures of certain streptococci joint lesions could be produced in animals. This result was, however, not constant. With small doses the joints became swollen, and later went on to suppuration, the condition finally ending in death. With large doses a septicemia, sometimes attended with joint symptoms, was observed. Glaser[1] has also observed multiple arthritis in rabbits following intravenous injections of various strains of streptococci. Under ordinary circumstances intravenous inoculations of the lower animals with virulent streptococci give rise to a rapidly fatal septicemia, but if cultures of attenuated cocci are injected either a monoarthritis or polyarthritis may follow. The latter result is variable.

A spontaneous endocarditis following intravenous inoculations of streptococci is, perhaps, even rarer than arthritis. Weichselbaum,[2] in a series of experiments, found it necessary to injure the heart valves before vegetations could be obtained, and although Pasquale[3] was able to produce subcutaneous abscesses, general septicemia, hemorrhagic infarctions of the lung, phlegmonous edema and hydropericardium in thirty-eight rabbits after subcutaneous and intravenous injections of streptococci from many different sources, he does not mention the occurrence of either arthritis or endocarditis. Widal and Bezancon[4] obtained a streptococcus from the mouth which gave rise to acute endocarditis in a rabbit after subcutaneous inoculations. In ninety-five experiments made with other streptococci this result was not again met with.

One noticeable feature of all these observations is the variation which many of these organisms show in their virulence for men and animals. Streptococci which produce fatal septicemia in human beings may show very slight virulence for animals, while organisms grown from local abscesses may be rapidly fatal for animals.

In view of the fact that streptococci isolated from sources other than the blood or complicating lesions from cases of rheu-

[1] Verhandl. des XII. Cong. f. inn. Med., 1901, p. 471.
[2] Ziegler's Beitrage, 1889, Bd. iv.
[3] Ibid., 1893, Bd. xii. p. 433.
[4] Le semaine méd., 1894, p. 195.

matic fever do, under certain circumstances, produce arthritis and endocarditis in animals when injected intravenously, it is surprising that the English observers particularly have made so few experiments to control their work. This side of the question needs to be thoroughly investigated before definite conclusions can be drawn as to the specificity of the streptococcus described as the cause of rheumatic fever. Indeed, several observers, among others Menzer,[1] believe that rheumatic fever is caused not by a specific coccus, but by many varieties of streptococcus.

Most observers are agreed that it is impossible to obtain a growth of bacteria either from the blood or joint fluids of cases of rheumatic fever which recover. Phillip[2] has recently reported such a series of negative results, and in cases of rheumatic fever reported from the Johns Hopkins Hospital by McCrae[3] cultures from the blood and joint fluids never gave a growth of streptococci. Except in the fatal case reported, we have had the same experience at the Pennsylvania Hospital. One must not overlook, therefore, the possibility of a streptococcus infection supervening as a terminal event in the fatal cases of rheumatic fever. Under these circumstances the condition might be similar to that which one finds in scarlet fever and variola.

SUMMARY. In a fatal case of rheumatism, endocarditis and chorea a streptococcus was isolated from the blood before death. This organism did not differ materially from the common varieties of streptococcus pyogenes in cultural properties, but produced very characteristic lesions in rabbits when injected intravenously. Such inoculations were always followed after a few days' incubation period by a multiple arthritis, which usually started in the ankles. In one rabbit extensive vegetations were found on the mitral valve, while typical infarctions were seen in the spleen and kidney.

We believe that this streptococcus is the same as that described by Wassermann, Meyer, Poynton and Paine and Ainley Walker, and considered at least by the last three observers to be the specific cause of rheumatic fever.

[1] Loc. cit. [2] Deutsch. Arch. f. klin. Med., 1903, Bd. lxxvi. p. 150.
[3] American Medicine, August 8, 1903.

DIFFUSE DILATATION OF THE ESOPHAGUS DUE TO CARDIOSPASM.

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DURING the past few years there has been considerable discussion by American, German, English and Swedish writers concerning diffuse dilatation of the esophagus without demonstrable anatomical stricture. Most of the reports have been made as the result of pathologic findings, the post-mortem review of the cases giving to us a history and symptoms of definite diagnostic value. The term "idiopathic dilatation" has been applied in most instances to this affection, but we prefer to speak of it as diffuse dilatation due to cardiospasm in presenting these two cases, which in their history, symptoms and findings upon clinical examination resemble in many respects the cases reported by Rumpel,[1] Sievers,[2] Zinnser,[3] Rosenheim,[4] Swain,[5] Lockwood,[6] Meltzer,[7] Gregersen,[8] Johnson[9] and others.

As far back as 1841 Malrustens[8] described a case of diffuse dilatation of the esophagus without stricture, and a year later Huss[8] reported a similar case. Zenker and v. Ziemssen[10] made an exhaustive study upon this subject, and Krause,[11] Kronecker,[11] Openkowski,[11] Netter,[12] Mikulicz,[11] Mehnert,[13] Rosenheim[4] and others have advanced theories as to the etiology of this interesting condition.

The first case which came under notice was an actor (C. G. G.), aged thirty-three years, who had been suffering from dysphagia since he was twelve years old. He gave a family history of tuberculosis and neurotic disturbances. He escaped the more serious infections of early childhood, but was a very nervous and poorly developed youth. He had a highly neurotic temperament and indulged in excessive sexual intercourse. He has had symptoms of internal hemorrhoids for the past twelve years.

When twelve years of age, while eating his supper, he suffered from a sudden attack of dysphagia and immediately thereafter forcibly regurgitated all he had eaten. He described his symptoms as follows: While in the act of swallowing solid food he felt a sensation of acute obstruction in the esophagus, behind the middle of the sternum. His face became flushed and he felt as if his heart had stopped beating, followed by palpitation. He threw off the food without nausea and the sensation of stoppage back of the sternum ceased immediately. He made several unsuccessful attempts to swallow both liquid and solid food and finally gave up in despair. Four or five days later he discovered that by gulping down a large amount of liquid after taking solid food he was able by considerable exertion to force the material into the stomach. For fifteen years this had been his method of feeding himself. At times he had been able to swallow with comparative ease, but at no time was he entirely free from dysphagia. Certain articles of food increased the difficulty of swallowing. The alternating of very hot and very cold liquids facilitated overcoming the resistance. At times the dysphagia was so great that no food would enter the stomach. If any remained in the esophagus it usually was regurgitated immediately or within a few hours. During sleep food remaining in the esophagus ran from his mouth. If he assumed the horizontal position immediately after eating, without attempting to force the food into the stomach, there would ensue an irritating cough, which was relieved only by emptying the esophagus either through the mouth or into the stomach.

The first examination was made on October 10, 1895, at which time the patient was directed to regurgitate. The contents of his esophagus were found to consist of mucus mixed with a small amount of his breakfast. Chemical examination showed the presence of lactic acid, but no hydrochloric acid was present. An esophageal bougie was passed readily down to the cardiac orifice, where resistance was encountered by the largest sized olive tip. By employing a moderate amount of pressure the bougie was passed on into the stomach. The flexible rubber stomach tube was passed for seventeen inches, when resistance was encountered, and the tube apparently doubled upon itself. Persistent attempts were unsuccessful in overcoming the resistance. On washing out the esophagus with tepid water, it was found to contain a large quantity of mucus and a small amount of food. A definite quantity of solid and liquid food was administered and two hours later the patient was able to regurgitate the entire amount. In order to determine whether or not any of the food passed into the

stomach, the potassium iodide and salol tests were applied, with negative results. On the following day the patient was given a potassium iodide and a salol capsule, together with an ordinary meal, and was asked to force them into the stomach. Immediately after taking the food he gulped down first six ounces of hot tea, then six ounces of iced milk, and, finally, six ounces of ice-water. He then took a deep breath, forcing the diaphragm well down, bent forward and compressed the sides of his chest with his hands. During this time he was swallowing in rapid succession. Suddenly the obstruction to the food gave way, and the patient's face, which had been very flushed, became pale and tears ran from his eyes. He complained of exhaustion and palpitation. In ten or fifteen minutes he felt perfectly normal and stated that this had been his method of feeding during the past fifteen years, sometimes accomplishing it with greater ease, sometimes with greater difficulty; that the effort always exhausted him and that the passage of the food into the stomach caused considerable pain. The potassium iodide and salol tests showed that the absorption and the motor power of the stomach were normal.

Three months later a repetition of the tests and physical examination did not reveal any material change in the patient's condition.

He was not seen again for eight years, during which time he led an active life, with irregular habits. His weight varied but slightly, around 109 pounds. The following examination was made in September, 1903: A tube was introduced into the esophagus and twenty-eight ounces of mucus and saliva, containing small particles of food eaten at dinner the evening before and at breakfast the day of the examination, were withdrawn. The esophagus was carefully washed out until entirely free from mucus, and a flexible rubber stomach tube with fenestrations extending upward for a distance of ten inches from the tip, and containing within its caliber a smaller tube, the eye of which was in direct apposition with the eye at the tip of the larger tube, was introduced and passed downward for a distance of seventeen inches, when resistance was encountered and the tube apparently doubled upon itself. By means of a long flexible whalebone stylet passed through the caliber of the smaller tube to within one and one-half inches of its tip, the resistance was overcome after two or three attempts and the tubes entered the stomach. A small quantity of fluid which was siphoned off contained free hydrochloric acid, combined acids and pepsin. No evidence of sacculation could be found on introducing a third tube and directing its tip in various directions by means of the stylet. After the third tube had been inserted for a distance of seventeen inches, twelve ounces of a weak aqueous solution of eosin were introduced through it and the tube was withdrawn. Five minutes later six ounces of the eosin solution were siphoned through the smaller stomach tube, showing that the fluid had passed into the stomach through the fenestrations of the larger tube. The patient was then given sixteen ounces of water to drink, and later eighteen ounces of water and mucus were obtained from the esophagus by siphonage. The coffee

test was not applied. A light meal was given, and the patient requested to force it into the stomach. This he accomplished by the method described above. The esophagus was then washed out and was found to contain very little of the food taken. The patient was directed to irritate the posterior pharyngeal wall with his finger in order to produce nausea, and, although he gasped and went through the muscular effort of vomiting, nothing was thrown off except mucus from the esophagus, showing that the cardia was in a spastic condition against both normal and reverse peristalsis. The capacity of the dilated esophagus was measured by having the patient drink water until he felt it regurgitate into the mouth. Thirty-two ounces were drunk before he experienced any unpleasant sensation, and after a few moments he was able to regurgitate with the greatest facility thirty-four ounces of water mixed with mucus. While the fluid still remained in the esophagus a rather indefinite area of dulness could be mapped out between the sixth and tenth dorsal vertebræ, extending three fingers' breadth to the left of the spinous processes. The *x*-ray and the esophagoscope were not used in this case.

Physical examination of the patient at this time revealed a floating kidney on the right side, a moderate degree of gastroptosis and heart action, which was rather slow, especially for one of his extremely nervous temperament.

The second case was F. P., a single woman, aged thirty-three years, with a good family history free from anything suggestive of a neurotic tendency. She had spent most of her life in the country, and did heavy housework. She was a large-boned, muscular woman, with a normal weight of 166 pounds. When she first came under observation, on November 20, 1902, she stated that eight months previously she experienced at times a choking sensation just behind the middle of the sternum when swallowing certain articles of food, such as tough meats, especially if they were cold. In order to relieve this sensation of stoppage she would regurgitate a portion or all of that which she had eaten. These attacks grew more frequent, and she soon found that it was only by restricting her diet to very hot liquids and thin gruels that she was able to obtain any nourishment. Regurgitation became more frequent as the dysphagia increased in intensity. The sensation of stoppage was usually so severe as to cause immediate regurgitation, but at times it was so slight that she felt as though the food had entered the stomach. Later, however, and mostly at night while she was asleep, this food would be regurgitated without her being awakened. Her general condition remained fairly good until two months after the onset of symptoms, when she was awakened at night by a sensation of choking and constriction behind the sternum. Her heart was palpitating and she felt faint. Taking a drink of cold water she immediately regurgitated and experienced relief. From this time on the symptoms of dysphagia increased, with occasional periods of alleviation. Her menses ceased, and up to the present, a period of twenty-six months, have not reappeared.

She became weak, emaciated and extremely nervous. The esophageal

capacity increased, and she was able to take larger quantities of food before being compelled to regurgitate. She fed herself on very hot liquids, and then gruels in small quantities at frequent intervals. Most of this was thrown off as soon as the collection in the esophagus was large enough to cause her discomfort. Portions of solid food would remain in the esophagus for twenty-four hours. She never experienced any nausea or actual pain, nor did she think that there was ever any true vomiting. She was not able, as was the previous patient, to force the food into the stomach by muscular effort. When first examined she was extremely emaciated, weak and very nervous. Clinical examination excluded any organic disease and discovered that the heart action was abnormally slow (42 to 54).

Her examination, extending over a period of several days, consisted of the following procedures:

1. A stomach tube was passed, meeting with resistance when the toothmark was six inches from the mouth. The tube bent on itself and coiled up in the esophagus. A large quantity of mucus mixed with food was withdrawn through the tube. It contained lactic acid, but no hydrochloric acid or pepsin. With this tube still in the esophagus, a second tube was passed, which reached the same distance from the toothmark, then met with the same resistance. After repeated attempts the resistance was felt to give way suddenly, the sensation being similar to that of making a false passage. Through this tube there siphoned out a small amount of fluid which contained hydrochloric acid and pepsin. In order to determine the position of the tubes eosin-stained water was introduced into one (supposedly in the esophagus) and plain water into the other. There was no communication between the tubes, as evidenced by the return of the unmixed fluids through their respective tubes.

2. Water was introduced through the esophageal tube until the patient complained of choking. Ten ounces seemed to be the capacity, but after a short period twelve ounces of water and mucus were obtained.

3. A tube with multiple fenestrations was introduced into the stomach and a plain stomach tube passed into the esophagus until resistance was felt at the same point as in the previous experiment. Eight ounces of eosin-stained water were introduced slowly through the esophageal tube, none of which could be recovered from the stomach.

4. An esophageal bougie was passed and the largest olive tip met with only moderate resistance at the cardiac orifice.

5. The patient was given a mixture of potatoes and bismuth subnitrate and a skiagraph was taken, which showed a doubtful increase in the shadow to the left of the sternum and posterior to the heart at a level of the fifth, sixth and seventh ribs.

6. By esophagoscopic examination the mucous membrane was found to be slightly congested, but no interruptions in the integrity of the esophageal wall could be discovered, nor were there any macroscopic changes at the cardiac orifice.

7. By auscultation over the esophagus and stomach the first sound in the act of swallowing was distinctly heard, but the sound caused by the passage of food through the cardia could not be detected.

In observing the patient carefully over a period of several days, it was found that although she experienced a sensation of pressure and burning behind the ensiform, yet she did not regurgitate her food until a definite amount collected in the esophagus. Sometimes food taken would be recovered by the esophageal tube forty-eight hours after being swallowed. Moderate distention of the esophagus with food gave rise to a harassing cough whenever the patient assumed the horizontal position, especially at night. The cough was relieved only by regurgitation. This symptom was described by Westphalen[14] as occurring in a case of his and was looked upon by him as of diagnostic value.

The patient was given the following treatment: No food, either liquid or solid, was allowed by mouth. Twice daily she was fed by means of the stomach tube and the esophagus was washed free from mucus. It was impossible, from the first, to pass a soft rubber tube into the stomach unless a second tube was passed into the esophagus to give it support. The irritability of the esophagus increased daily, until finally a flexible tube could not be forced through the cardiac orifice. A tube was then passed by means of a stylet and allowed to remain, with the hope that the continuous dilatation would influence favorably the contractility of the cardiac orifice. The tube caused so much discomfort that it was removed at the end of forty-eight hours, and the result was negative. Thereafter the stomach tube was always passed by means of a stylet, the patient being taught to pass it and feed herself twice daily.

During the following three months the retaining capacity of the esophagus was reduced to two ounces. The patient continued this method of feeding for a period of seven months at home. She gained in weight and at times was able to swallow liquids without much difficulty.

She returned in December, 1903, when Dr. Martin etherized her and dilated the cardiac orifice with a specially devised instrument. The instrument consists of a metallic shaft the same length as that of an ordinary esophageal bougie, at the end of which there is a dilating bulb made of six flexible steel plates so arranged that by turning a handle at the proximal end of the shaft the distance between the ends of the flexible plates is shortened and the caliber is increased to 120 mm. in diameter. The instrument is introduced through the esophagus into the stomach and the dilating bulb run up to 100 mm. and withdrawn through the cardiac orifice. The principle of the instrument is the same as that of the Kollmann urethral dilator.

We feel sure that repeated use of this instrument will bring about a partial paralysis of the cardia, but we temporarily discontinued its use because of our desire to put the esophagus at complete rest and at the same time force the patient's nourishment and resorted to a gastrostomy.

After this dilatation the patient was able to swallow small amounts of liquids

and in some instances a little solid food, but in a few days the spasmodic condition returned and she regurgitated everything. At this time she vomited the gastric contents on two or three occasions. The retaining capacity of the esophagus was two ounces, which increased to eight ounces within a few days after she began to take food by mouth. Tubal feeding was again resorted to, but it caused so much irritation of the esophagus that it became necessary to perform a gastrostomy on February 26, 1904, when it was found that with the patient partially anesthetized the cardiac orifice easily permitted the introduction of two fingers.

Since then she has been fed through the gastric fistula, and she has not been allowed any food, either solid or liquid, by mouth. The method of feeding has been as follows: Six feedings in the twenty-four hours. At 6 A.M., two eggs with six ounces of milk; at 9 A.M., four ounces of cream; at noon, six ounces of emulsified food; at 3 P.M., six ounces of beef-juice; at 9 P.M., six ounces of beef-juice. The emulsified food consists of meat, potatoes, bread and butter and one other vegetable. It is thoroughly masticated and then beaten up with two raw eggs and a small quantity of broth and strained. The patient has gained an average of five pounds weekly since this method of feeding has been instituted.

In each of these cases a diagnosis of diffuse dilatation of the esophagus, with spastic contraction of the cardiac orifice of the stomach, was made.

In the case of the man the diagnosis was comparatively simple. He was neurotic. The dysphagia was sudden in its onset and was increased by the taking of certain articles of food. There was regurgitation without nausea and a sensation of burning pressure back of the ensiform. The following facts point to cardiospasm and diffuse dilatation of the esophagus: the food running out of his mouth when he was in the horizontal position; the variations in the degree of the dysphagia; the regurgitated material consisting of the food last eaten; the uniform findings on the passage of tubes; the introduction of an esophageal bougie into the stomach without much difficulty; the suddenness with which the tube entered the stomach when the resistance gave way; the change in the amount of resistance; the negative Rumpel's double-tube test; the inability to vomit; the absence of the second sound heard in swallowing and the ability of the patient to overcome the obstruction by mechanical means which have an influence upon the nervous mechanism of the esophagus and cardia.

In the case of the woman the onset was insidious. She was not neurotic and was free from the stigmata of hysteria. The inability to overcome the obstruction by voluntary effort, the positive result of Rumpel's double-tube test and the regurgitation of accumulated food products all pointed to a diagnosis of either a sacculation or a diverticulum of the esophagus. The variation in severity of the symptoms, the fixed point of resistance encountered in the passage of tubes, and the sudden cessation of resistance to continued pressure of the tube without changing its position, the absence of the second sound in swallowing, and the inability to vomit when nauseated suggested cardiospasm. The vomiting on two or three occasions, and the coincident ability to swallow food succeeding the forcible overstretching of the cardia, together with the short duration of this condition, indicated temporary paralysis of a spastic cardia.

Meltzer[7] first pointed out the diagnostic importance of the inability to vomit in cases of cardiospasm, while Leichtenstein and Rumpel report cases in which this symptom was observed, although in their cases true stomachic vomiting appeared at intervals.

The symptoms indicative of diverticulum are compatible with a diagnosis of cardiospasm when the pathologic condition is one in which the cylindrical dilatation at the extreme lower end of the esophagus has spread out over the dome of the diaphragm, forming a circular gutter, the bottom of which lies below that portion of the esophagus blending into the cardia. This explains the positive result of the double-tube test, the diverticulum type of food regurgitation, and the inability to force food into the stomach by muscular effort.

The recovery of water introduced into the esophagus while a tube is in the stomach, by simply withdrawing the tube, negatives diagnosis of diverticulum. In the latter condition it would be necessary to manipulate the tip of the tube until it entered the pouch. Moreover, in diverticulum, symptoms of obstruction do not supervene until the sac is filled. The passage of a full-sized bougie excludes organic stricture. The age of the patient, duration of symptoms and physical examination exclude obstruction from malignant disease, tumor or abscess.

The etiology of this affection has been much disputed; the older writers have ascribed it to a primary weakness or a lessened resistance of the esophageal wall. They emphasize the necessity of a congenital defect, although admitting the possibility of its being an acquired condition; but autopsy findings disprove their views by disclosing hypertrophy of the muscular coat in the majority of cases. Mehnert[13] attributed the condition to abnormalities in the position of the aorta and the esophagus. Mikulicz[11] and Meltzer[7] advanced the theory of a primary cardiospasm resulting from a failure of the central inhibitory influences controlling contraction of the cardia. Rosenheim[4] opposed this view after noting that little or no resistance was encountered in sounding cases of undoubted dilatation of the esophagus, and that in cases of organic stricture of the cardia there was no such marked dilatation of the esophagus. He promulgates the theory that the predisposition to idiopathic dilatation results from a weakening of the muscular coat. F. Krause[11] takes a position midway between these two views, and looks upon the condition as a functional disturbance of the innervation of the esophagus, causing not only the cardiospasm but also a weakening in the muscular wall. He supports his view by the result of Kronecher's animal experiments, in which the pneumogastric nerve was cut, causing cramp-like contraction of the cardia, paralysis of the muscular wall and secondary dilatation of the esophagus. He further strengthens his position by reporting a case of idiopathic dilatation of the esophagus in which degenerative changes of the pneumogastric nerve were found at autopsy. Lossen considers Krause's theory incomplete, because it does not explain those cases in which the dilatation occurs in the extreme lower end of the esophagus, forming, as it were, an ante-stomach, and in which there is no cardiospasm. Primary inflammation of the mucous and muscular coats has been given as a cause, but those inflammatory changes found are secondary rather than primary.

The age of the patients, the acute onset and the clinical findings lead us to the view that in our cases the cause is cardiospasm. The etiology of the spastic condition seems best explained by Kronecher[11] and Openkowski,[11] who succeeded in isolating branches of the vagus controlling the contractility of the cardia, both inhibitory

and accelerative. The tonicity of the cardia is the resultant of two forces—contractile and inhibitory. The former is due in part to the influences of the central nervous system exerted through the branches of the vagus, and in part to an inherent quality of the musculature of the cardia itself, as is shown by the rhythmical and powerful contraction of the excised cardia of a rabbit. The inhibitory influences come through the branches of the vagus distribution, and when they are removed the contraction of the orifice occurs. In the act of swallowing an inhibitory impulse is set free which opens the cardia by decreasing its tonicity. As the food enters the orifice the inhibitory influence ceases, contraction takes place and the food enters the stomach. The lack of inhibition may be due to degenerative changes in the vagus, as noted by Krause,[11] or to reflex disturbances from distant foci of irritation. Lockwood[6] calls attention to the importance of considering reflex irritation of the vagus by the abdominal nerve supply through the branches of the semilunar ganglion. In the case which he reports dysphagia appeared coincidently with a floating kidney, the result of traumatism.

In both of our cases pathologic conditions exist in the abdomen which might produce reflex irritation. The man has a floating kidney, and in the woman the cessation of the menstrual functions occurred simultaneously with the onset of the dysphagia.

In making the diagnosis of cardiospasm with diffuse dilatation of the esophagus the history of the patient is of paramount importance. It usually occurs in neurotics from twenty to forty years of age. The onset of dysphagia is sudden and is accompanied by a sensation of burning and stoppage posterior to the sternum. At first the difficulty in swallowing is caused only by solid and insufficiently masticated food. As the disease progresses the difficulty increases. At times no food can be swallowed; at other times certain articles, such as very hot liquids or ices, pass into the stomach without any voluntary exertion. At irregular intervals the symptoms may disappear entirely.

Pain is a variable symptom and is dependent upon the degree of secondary esophagitis.

The regurgitation of food is characteristic; it occurs immediately

or very shortly after eating and gives immediate relief to the symptoms of obstruction. The regurgitated material is composed of the food last taken. In advanced cases with marked dilatation food may be retained for many hours without causing discomfort. Any food remaining in the esophagus will be regurgitated whenever the patient assumes a horizontal position, especially during sleep. This sign in connection with a dry cough, which occurs at night on assuming the recumbent position, and which is relieved only by regurgitation of food, is regarded by Westphalen and others as characteristic of diffuse dilatation of the esophagus.

The absence of true vomiting and the inability to raise flatus have been noted as symptoms of cardiospasm. The majority of cases are enabled to swallow food with exertion or by employing definite mechanical assistance. With a few all that is necessary is to go through some gymnastic effort, while others force the solid food into the stomach by gulping large quantities of either hot or cold liquid, the amount usually corresponding to the capacity of the dilatation. In other instances the drinking of water previous to the ingestion of solids has proven successful.

The clinical examination of these cases establishes the diagnosis. The easy passage of the esophageal bougie excludes organic stricture. The uniform point (38 cm. to 39 cm. from the incisor teeth) at which resistance is encountered, and the sudden giving way of this resistance, followed by the further passage of the stomach tube, indicates spasm at the cardia in contradistinction to diverticulum. The emptying of fluids contained in the esophagus by the mere withdrawal of a tube from the stomach without further manipulation indicates a diffuse dilatation as against diverticulum. The chemical examination of regurgitated material reveals the presence of lactic and butyric acids, an absence of free hydrochloric acid and pepsin, failure of proteid digestion and complete conversion of starches into sugar.

A large quantity of mucus is always present, but is not distinctive of dilatation. The morphologic features of the material regurgitated from a diverticulum and from a diffuse dilatation differ, because of the length of time the food is contained. In cases of diverticulum food particles are found which were eaten

several days before and decomposition is more advanced than in cases of dilatation.

Rumpel's double-tube test differentiates diverticulum from diffuse dilatation, but is liable to error when the dilatation occurs in the most dependent portion of the esophagus. The substitution of the second sound of the act of swallowing (Durchpressgeraüsch) by a sound resembling liquids falling into a cavity containing fluid is indicative of the diffuse dilatation of the esophagus with spastic cardia.

Meltzer's alcohol and atropin test, Rumpel's litmus reaction, Einhorn's coffee experiment and the potassium iodide test all may be employed to determine the permeability of the cardia.

The dulness elicited over the chest posteriorly when the esophagus is filled with a liquid, together with a shadow obtained in the skiagraph when a mixture of bismuth is employed, may aid in determining the size and position of the dilatation.

The esophagoscope may be used to eliminate organic change of the cardia and diverticulum.

The treatment of this condition depends upon the character of the case. In those patients who are able to force food into the stomach little is required, except lavage to combat the tendency to acute esophagitis; but in those cases in which total obstruction is periodic or permanent, nourishment must be administered by systematic tubal feeding, and this entails the danger of producing acute esophagitis.

In the few cases in which the cardiospasm is so marked that the passage of an ordinary stomach tube is impossible a flexible whalebone stylet may be used to give the necessary rigidity. If tubal feeding becomes impossible, due either to an esophagitis or to increased spasm, rectal feeding may be employed to relieve irritation, or preferably gastrostomy may be performed. Gastrostomy is not curative, but it gives the esophagus complete rest and permits of forced feeding.

Electricity, passage of bougies and retrograde sounding have been advised, but have proven unsatisfactory.

The rational treatment is a repeated overstretching of the cardia in order to destroy its tonicity. This may be accomplished with

accuracy by the instrument used in one of our cases or by the pneumatic bag devised by Lockwood.

The prognosis as to complete restoration of normal activity is bad, but the condition, though pitiable, is not necessarily hopeless. Years intervene between the onset of the symptoms and death, which usually results from intercurrent disease.

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IDIOPATHIC DILATATION OF THE ESOPHAGUS: CARDIOSPASM.

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Dr. Sippy presented a specimen of idiopathic dilatation of the eosophagus, together with x-ray photographs of two other cases observed.

Following is an abstract of the clinical and pathologic findings of the case from which the specimen was removed:

The patient, a woman, aged forty years, came under observation in April, 1904, two weeks before death. As a child, always healthy. Sepsis followed miscarriage twelve years ago. No gastrointestinal disorders. About five years ago patient began to have choking sensation while eating. These sensations continued, with varying intensity, for three years and were attributed to *globus hystericus*. At times food would return to the mouth shortly after it was swallowed. About two years ago the choking sensations became more regularly associated with regurgitation of food during and following meals. It was supposed that the food was vomited. There was no nausea, no retching. The food returned was not sour. Distress behind the lower part of the sternum while eating was frequently noted. Solids were retained better than liquids. The trouble was worse when she was nervous.

About a year ago the difficulty became aggravated and patient began to lose weight. Her normal weight was 140 pounds. In December, 1903, she was reduced to 116 pounds.

The cause of her trouble was unrecognized. A surgeon of unusual merit performed gastroenterostomy, believing that pyloric obstruction existed. For a short time following the operation patient experienced less discomfort upon eating, but did not gain in weight. Soon after operation the condition was as before. Discomfort, amounting to actual pain, at level of lower part of sternum while eating; vomiting (regurgitation) of food during and subsequent to meals became more marked; awakened often during the night to find pillow flooded with food and drink. Horizontal position favored regurgitation of food.

In April, 1904, patient came under observation of the author. Weight of patient, 98 pounds. The manner in which food and drink were returned made diagnosis of esophageal obstruction easy. It was possible to introduce 500 c.c. of liquid into the esophagus and regain practically all by aspiration.

During first examination stomach tube was arrested fourteen inches from the incisor teeth; after resting there a moment it passed into the stomach. Later neither a large nor small-sized bougie would pass the obstruction.

Oatmeal gruel, containing 10 per cent. bismuth subnitrate, was introduced into the esophagus and *x*-ray photographs were obtained, showing dilatation at lower part of the esophagus.

Olive oil would not pass the seat of obstruction.

Microscopic examination of contents of esophagus aspirated showed epithelial cells, bacteria, but very few red cells and leukocytes. No pus present.

The diagnosis of idiopathic dilatation of the esophagus from cardiospasm was made. Absolute rest, rectal feeding, bromides per rectum, local anæsthetics to cardia, etc., had no influence on the spasm. Death from inanition the apparent termination. Gastrostomy was urged for relief. Symptoms of intoxication from inanition appeared. Gastrostomy was successfully performed by Dr. Bouffleur. Liquid food was abundantly supplied, but delirium and finally coma appeared, and death took place eighty-four hours after operation.

Autopsy showed pylorus and duodenum normal. No hypertrophy of muscles of pars pylorica. No evidence of recent or old obstruction at pylorus. Gastroenterostomy opening admitted two finger-tips. Gastrostomy wound perfect. No anatomic narrowing at the lower end of the esophagus. The musculature at the cardiac orifice of the esophagus not appreciably hypertrophied. The adjacent esophagus for distance of 1½ to 2 cm. above was normal. Uniform dilatation began at this point and gradually increased upward.

The seat of greatest dilatation was from 6 to 12 cm. above the cardiac orifice; from here upward dilatation gradually grew less, till the upper end of the esophagus was reached.

Where the dilatation was greatest the mucous membrane was thrown in longitudinal folds from 6 to 10 mm. in depth. Transverse folds were also present.

At the lower end of the sacculation the musculature of the esophageal wall was only slightly hypertrophied. At the point of greatest dilatation the circular fibers alone were 5 mm., the longitudinal fibers 2 mm. in thickness. (Normally the total thickness of the esophageal muscle is from 0.5 to 2.2 mm.)

From here upward the hypertrophy gradually diminished. At the upper end of the esophagus the muscular wall was visibly thickened. The mucous membrane was not eroded. No scar tissue was present indicative of previous ulceration. At the autopsy the largest sized bougie passed the cardiac orifice without using much force.

Anatomically there are two forms of idiopathic dilatation of the esophagus: (1) dilatation without hypertrophy of the muscular wall of the sac, and (2) dilatation with compensatory hypertrophy of the muscular wall. This case belonged to the latter, which is by far the more common class of cases.

IDIOPATHIC DILATATION OF THE ESOPHAGUS.

By FRANCIS P. KINNICUTT, M.D.,
OF NEW YORK CITY.

In illustration of the rare and interesting lesion of the esophagus, which has been fully described, together with a review of the literature of the subject, in the papers of Dr. Tyson and Dr. Sippy, I am able to present to the Association a specimen of unusual interest. It is one of diffuse and extreme dilatation of the esophagus in its entire length and also of moderate dilatation of the stomach. Macroscopic and microscopic examinations fail to reveal the presence of any anatomic cause for the dilatation of the esophagus, and in the absence of such cause it is justifiable to consider it as an idiopathic dilatation.

The stomach at operation was found to be dilated and dislocated. The pylorus was thickened and moderately stenosed, admitting the tip of a forefinger of average size. The hypertrophy was believed to be of a benign character, an opinion which was confirmed by microscopic examination of the tissues after death.

The patient was admitted to the Presbyterian Hospital in the service of one of my colleagues in the autumn of 1902. In the history of the case it is stated that difficulty in swallowing and regurgitation of food first occurred twenty years before the patient came under observation; that these symptoms were constantly present for a period of a year and that a diagnosis of esophageal spasm was made at the time.

The further history was one of more or less constant digestive disturbances, with periods of more acute distress accompanied by vomiting of large quantities of food and fluids, often of food taken one or two days previously. Physical examination on admission to the hospital gave the signs of tissue changes in the left lung. The dulness noted, extending outward and to the left of the upper dorsal vertebra, was undoubtedly partially due to the enormously dilated esophagus. The lower border of the stomach, after inflation, was demonstrable 3 inches (7.7 cm.) below the lower lip of the umbilicus in the median line; the upper border was not definitely made out.

Examination of the gastric contents one hour after Ewald's test breakfast showed combined HCl in diminished amount and an absence of free HCl. Lactic and butyric acids were present in large amounts.

Examination of the blood gave red cells 4,792,000; white cells, 10,500; hemoglobin, 85 per cent.; color index, 95.

Tubercle bacilli were not found in the sputa.

The patient was under observation in the medical wards for several weeks. During this period lavage was used daily, with slight amelioration of the symptoms. There was at no time the slightest difficulty in introducing a full-sized stomach tube into the stomach, and the presence of combined HCl in the contents removed indicated that the tube passed through the cardia.

Esophageal dilatation was not suspected. The symptoms were believed to be due to dilatation of the stomach, the result of pyloric stenosis. As the nutrition of the patient steadily deteriorated in spite of treatment, a gastroenterostomy was advised and performed by Dr. McCosh. The patient's condition temporarily improved; but later the patient rapidly failed, and died seven weeks after the operation.

Autopsy. Macroscopic and Microscopic Findings. The lesions were practically confined to the left lung, the esophagus and the stomach. The lesion of the lung consisted of a chronic interstitial pneumonia, with numerous small cavities in the lower lobe. The esophagus, which I am able to present to you for examination, is 18¾ inches long (47½ cm.), and is greatly dilated in its entire length. At its junction with the pharynx, at the border of the cricoid cartilage, it is of normal size; it immediately begins to enlarge, and 2 inches (5 cm.) below the cartilage is moderately distended, the diameter being 4 inches (10 cm.); this size it maintains to a point 10 inches (25½ cm.) from the cartilage, thence it very gradually and symmetrically diminishes in diameter, the whole pouch presenting the fusiform appearance usual in primary dilatations. At 12½ inches (32 cm.) below the cartilage the diameter is 2.9 inches (7½ cm.), and just above the cardiac orifice it is 2.2 inches (5.2 cm.). The diameter of the cardia is two-thirds of an inch (1.5 cm.). The walls are uniformly thickened; at a point midway between the origin of the esophagus and the cardia the wall is 5 mm. in thickness. In the fresh state the capacity of the esophagus was 1800 c.c. of fluid; that of the stomach, 2000 c.c. After the tissues had been hardened and lost their elasticity in formalin, the capacity of the esophagus was reduced to 1300 c.c. and that of the stomach to 1100 c.c. On opening the abdomen the stomach was found to be moderately dislocated and dilated. The lower border reached a point about 3 inches (7½ cm.) below the umbilicus in the median line. No growths were present in the esophagus, stomach, duodenum, in the tissues contiguous to them or elsewhere in the body. No scar tissue was anywhere observed.

Microscopic Findings. Sections from many portions of the esophagus, from the cardiac orifice and from the pyloric ring show a moderate degree of hyper-

trophy, especially of the vessels of the connective tissue. The longitudinal and circular muscle fibers seem to preserve their normal proportions. The wall of the cardiac orifice shows notable thickening as compared with the walls elsewhere. Brunner's glands are numerous. The gross appearance of pyloric thickening is due to a moderate degree of hypertrophy of muscle tissue, to hypertrophy of Brunner's glands (increase both in number and size), and to an increase in the thickness of the submucous and peritoneal layers of connective tissue.

The findings at autopsy in connection with the history of the case would seem to justify the conclusion that the esophageal dilatation occurred at the period when the symptoms of dysphagia and regurgitation of food were first noted, twenty years before the patient came under observation in the hospital, and that the dilatation once effected probably continued to increase for an indefinite period and was largely the cause of the symptoms noted up to the time of death. The pathogenesis of the original dilatation is necessarily a matter of speculation. It may be conceived to be due either to a spasm of the circular fibers of the cardia, a motor neurosis, probably associated with an absolute or relative weakness of the esophageal musculature, or possibly to a functional paralysis of the longitudinal muscular fibers by the contraction of which the cardia is opened.

In either case a dilatation once effected would probably persist and increase even without the indefinite persistence of the spasm or paralysis through the lodgement of food in the dilated pouch.

The dilatation of the stomach is due to a simple hypertrophic stenosis of the pylorus, probably associated with an atonic condition of the gastric musculature. Simple hypertrophic stenosis of the pylorus, with consequent dilatation of the stomach, is generally believed to be due to persistent pyloric spasm induced by a hyperacidity of the gastric juice, which, in turn, is regarded as a secretory neurosis. Such a view may be accepted as a probable explanation of the hypertrophic stenosis present in the case under discussion. The hypochlorhydria noted in the present instance was undoubtedly a symptom of late development—that is, after a very considerable dilatation of the stomach had occurred as a result of the pyloric stenosis. Under such conditions a hypochlorhydria is to be expected, and is the rule.

DISCUSSION.

DR. JANEWAY: I have a case to report of which I have the picture, but the patient is living. The history is one of twenty years' duration of dysphagia, much the same history as Dr. Tyson's case, with this exception, that he had a complication of hemoptysis. He was supposed to have lung trouble for two reasons: that he had some dulness about the lower lobe of the right lung and some catarrhal trouble about the left, and he was sent to me because of the coughing and spitting of blood and the coincident vomiting of some food. Nothing was found to be wrong in the lungs. I attempted to give him a test breakfast, but promptly brought up the whole breakfast from the esophagus. I had him starve for a day and then take the test breakfast, and he brought up in addition to that breakfast some material which had been taken the previous day. Then I discovered that he could take 800 c.c. of fluid into the esophagus. He holds 500 c.c. without difficulty and this photograph was taken with that amount in. An 18 mm. tube will pass readily into the stomach, but you can feel the grasp upon it at the cardiac end.

There is no doubt that we have here one of the cases of simple dilatation. I had him on rectal feeding for a time to clear out the esophagus and relieve it from ulceration.

In looking over the history of these cases one finds two things: that there have been ulcers in the mucous membrane from which the blood comes and that some cases have been suspected of tuberculosis. The case is of interest on account of the showing of the possibility of making the mistake in diagnosis. He lost weight while on rectal feeding, but has regained it by using purees and meat ground very fine.

The mistake is often made in these cases of supposing them to be hysteric. I have a patient under observation now, a young lady, whose esophagus will hold between ten and twelve ounces, of which she will regurgitate ten ounces. I had hoped to bring a picture of her, but she is very nervous and begged off when I wanted to have it taken.

DR. MELTZER. I realize that it is late and I shall be brief, but I think I ought to say a few words in this discussion. The gentlemen were speaking of cardiospasm as a disease; they observed a few cases most of which were not recognized during life. I have a personal grievance in this matter. I was the one who introduced into pathology the conception of cardiospasm. I described the physiology of it and gave an ample description of the symptoms for the recognition of this condition. From what I have heard to-day I see that I and most of what I have said on the subject have been forgotten. Until 1888 the literature on the pathology of the esophagus knew only idiopathic dilatations of the esophagus and organic stenosis with secondary dilatations. I then

stated that there were cases of permanent stenosis of the cardia of a purely functional origin, due to an increase of the normal tonus, with secondary dilatation of the esophagus. I described such a case and tried to interpret several cases previously described as idiopathic dilatation. Of course, I shall not enter into details. Those who are interested in the subject will find my article in the *Berl. klin. Wochenschrift*, 1888, No. 8. I shall only add that my patient died some time ago and a partial autopsy was obtained. My diagnosis was confirmed in all particulars.

NOTES ON SOME UNUSUAL FORMS OF INFECTIOUS DISEASE OF THE CENTRAL NERVOUS SYSTEM.

By JAMES J. PUTNAM, M.D.,

AND

GEORGE A. WATERMAN, M.D.,
OF BOSTON.

THE first of these cases is an example of an unusual form of disease, characterized clinically by a progressive impairment of sensation and motion and spinal reflexes, spreading steadily upward so as to cause death in ten weeks and anatomically by a complete degeneration of the spinal structures, neither inflammatory nor anemic in origin.

CASE I.[1]—Male patient, aged thirty years; married; a hotel-waiter, with a history of good health and habits; not syphilitic, so far as known.

The disease began to show itself about February 1, 1903, the first symptom being numbness of the toes, soon spreading to the feet and ankles, and quickly followed by weakness of the leg muscles. A few days after this, while bathing his feet in hot water, the patient found himself unable to recognize the temperature distinctly. He continued at work for a fortnight, but with increasing difficulty. One day he fell on the street and two days later he gave up altogether and applied for admission to the Massachusetts General Hospital.

The examination made there on February 25th showed that his right leg was wholly paralyzed and the left almost wholly. The muscles were flaccid. The sensibility in all modes was seriously impaired for all parts below the waist and at the upper level some pain was felt. This impairment was greatest for the sacral nerve areas, especially the lower two, and it extended higher on the right half of the abdomen than on the left half.

[1] We are indebted to Dr. W. W. Gannett, the physician in charge of the case, for permission to utilize his hospital records.

The knee-jerks and Achilles reflexes were obtainable, but only very slightly on the right side. The plantar reflexes were normal, the cremaster absent. The bladder was paralyzed and distended at the time of entrance to the hospital, and the rectal sphincter was also paralyzed. Above the waist, motion and sensibility were normal. The mind was clear. The thoracic and abdominal viscera were normal, the spleen not enlarged. The white blood count was 19,000. The urine was of normal color, acid, 1022, free from sugar and bile, but containing the slightest possible traces of albumin. Urea 1.7 per cent. The sediment contained a few small round cells and a small amount of pus, free and in clumps, but no blood and no casts. In spite of the absence of a syphilitic history the patient was given iodide of potash and mercury.

Between this period and April 17th, a little more than seven weeks later, when the patient died, the signs indicated an uninterrupted extension of the disease upward, associated with an irregular fever, usually about three degrees lower in the morning than at night, frequently reaching 103° and occasionally 104°, while the pulse rate varied from 80 to 120 and was also higher at night.

By March 7th, that is about two weeks after entrance, the grasp of the hands had become feeble and the impairment of sensibility had reached the area of the eighth cervical nerve, but at that date the arms could still be moved freely at the shoulder.

On April 7th, one month later, he was unable to raise the arms above the head and the anesthesia was complete from the level of the third rib in front. At this date also the respiration became irregular and shortly afterward it was purely abdominal.

On April 11th, he became for the first time dull and half unconscious and showed some difficulty in swallowing and speaking, but death did not occur until six days later.

The leukocytosis and the cystitis or pyelitis both increased proportionately to the growing intensity of the disease. Thus on March 4th it is noted that during the past week the white blood count varied between 16,000 and 19,000. On March 10th it was 28,000, on March 12th it was 33,000. On this same date the urine showed considerable pus, occasional casts with blood adherent, renal cells and also small amounts of free blood. The amount of albumin in the urine, however, was still small, but from this time onward it increased. On March 10th he began to pass blood with the stools and to suffer from a bed-sore on the buttocks, both conditions being presumably due to disordered innervation. The temperature, pulse and respiration all became more elevated toward the last and finally, on April 17th, rales appeared in the chest and trachea and he died unconscious. During the week before his death he had had a number of slight chills.

The post-mortem examination was made by Drs. Wright and Richardson and with their kind permission we make the following abstract from their notes covering the condition of the nervous system. As regards the rest of

the examination it may be said that the kidneys showed signs of pyelonephritis and that the mucosa of the colon was here and there excoriated. The spleen was normal.

"The pia of lumbar and thoracic regions is opaque and shows all along its course in these regions a slight amount of yellowish-white, soft, fibrinous-like material. In the cervical region this is not apparent. The vessels of lumbar and thoracic regions are somewhat injected. Those of cervical region are not. On section through the thoracic region of the cord its tissue is soft, opaque and homogeneous in appearance.

"Culture on blood serum from heart and spleen sterile.

"Cover-glass from fibrinous material of cord pia shows no bacteria and no leukocytes.

"The brain was hardened in formalin and cut in several sections, but no lesion was discovered.

"After hardening in formalin the spinal cord shows the lumbar and greater portion or dorsal region transformed into mushy material with loss of markings.

"In the upper thoracic region and lower cervical region cavities with softened contents are present in the substance of the cord.

"Sections of cord prepared with Heller's method for myelin show extensive destruction and disintegration of cord, most marked in the lumbar and thoracic regions. At these levels the cord is extensively or totally transformed into an indefinite mass of disintegrated myelin and detritus. In places there is infiltration with large epithelioid cells, and these are also present around the nerve roots. There is no infiltration with leukocytes or small round cells."

Further sections were subsequently made by Dr. Waterman, an examination of which justifies the following additional statements:

The lower dorsal and lumbar levels stained by Weigert microscopically show practically no myelin except in a few of the posterior nerve roots. The cord here has wholly lost its structure, there being no demarcation between gray and white matter.

Microscopically there is no trace of normal cord structure left, but, instead of it, a mass of more or less closely packed fat granule cells with newly formed bloodvessels. The fat granule cells are round, mononuclear bodies of varying size, some being apparently swollen with drops of absorbed myelin, which at times stains faintly. Occasionally these cells appear to be proliferating from the capillary endothelium in various stages of cell division. These cells are also seen infiltrating the pia, especially around the nerve roots, causing considerable thickening of the membrane. The anterior roots are wholly degenerated, but some of the posterior roots appear normal and stand out in striking relief. The central canal of the cord is obliterated. The bloodvessels are filled with blood, but not abnormally so, and the vessel walls appear normal. No infiltration of leukocytes is seen around the vessels.

The sections from the upper dorsal region, stained by Weigert, show the

presence of myelin, though the disintegrated appearance of the cord is apparent macroscopically and the gray matter is indistinctly made out. Microscopically the white matter is made up of degenerating fibers in various stages of swelling and disintegration. There is a beginning invasion of fat granule cells of the type found in the lower levels. The anterior horns still show ganglion cells, though many of them are degenerated. A few cells are also left in Clark's column. Many of the nerve roots are degenerated.

The seventh cervical level shows distinct demarcation of the gray and white matter, the areas of degeneration being limited to the posterior and lateral tracts. Macroscopically this level resembles the picture seen in combined sclerosis, in pernicious anemia, etc. In the center of the degenerated area of the posterior columns there is a round cavity 3 mm. in diameter.

Microscopically the degeneration is limited to these tracts. The fat granule cells have not made their appearance. The anterior horn cells show no marked degeneration with the stains used. The central canal is normal. The nerve roots show no degeneration. The pia shows no infiltration with round cells. Higher levels of the cervical cord show only a degeneration of the posterior columns, most marked in the column of Goll (secondary degeneration).

At no level of the cord is there any evidence of an inflammatory condition, nor is there anywhere evidence of impaired circulation. The process then is one of degeneration of rather an acute form and not due to vascular change. Such a degeneration could be caused only by some toxic substance, but in its form and history it represents, certainly, an unusual type of disease. It is, of course, possible that the toxic material which caused the spinal degeneration was formed on the inflamed surface of the urinary tract, but this is unlikely in view of the trifling nature of this inflammation at the outset, while, on the other hand, it is easy to explain how the myelitic process should have given rise to the urinary change.

Reference has been made to the fact that the degenerations at the upper level of the diseased process were confined to the posterior and lateral tract areas, and that they resembled the degenerations found in connection with pernicious anemia and other forms of malnutrition, and occasionally independently of these disorders. It may be added that this resemblance is the greater for the fact that all along the margins of these degenerated areas the familiar "perforated card" appearances are seen, due to the subacute lateral extension of the process, and, literally, to the breaking down of nerve processes.

In the *Review of Neurology and Psychiatry* for June, 1903, a case is reported which, from a clinical standpoint, closely resembles the one here given, but anatomically it was characterized by striking inflammatory, that is vascular, disease.

Our knowledge of the infectious processes as a whole is so incomplete that we are far from wishing to assert that a fundamental

distinction is to be made between the cases where signs of inflammatory changes are present and those where it is lacking. Even clinically an ascending myelitis of so slow a course as this is rare, but another instance has just come to our notice in a case seen in consultation at the Massachusetts Charitable Eye and Ear Infirmary, and this is the more noteworthy from the fact that the onset of the myelitis was preceded by an intense optic neuritis with unusual swelling of the optic papilla, attended at first by few and only indefinite indications of disease elsewhere.

Although this case is of an unusual sort, yet it is, of course, to be recognized that diffuse spreading myelitis is by no means unknown clinically, and that, as regards the character of the lesion, this sort of degeneration without inflammation, strictly speaking, is clearly treated by Schmaus, in his masterly work on the *Diseases of the Spinal Cord*, as one of the processes of infectious origin. It is a matter of much doubt, as a matter of fact, whether a known inflammatory lesion of this kind even implies the action of a special agency. It is rather one of the modes in which the nervous system responds, it may be, to many toxins. It is very difficult, indeed, to excite inflammatory reactions in the spinal cords of animals, and nothing is more striking than to see in how many different ways the nervous system of different individuals respond to morbid influences which are apparently identical.

Case II.—The winter of 1902–03, during which the illness of the patient just spoken of occurred, was marked by the appearance of a variety of forms of infectious disease of the nervous system, of different sorts and in unusual number.

In the same ward with the patient already referred to there lay a man who was ill for a number of months with a progressive motor paralysis without sensory disorders, which spread upward so as to involve the deglutition and the motions of the face. The temperature and pulse were elevated and there was a moderate leukocytosis, but the case terminated in recovery at the end of six months. The spleen was not enlarged. No cause for the disease could be made out.

On the opposite side of the same ward was a third male patient who presented symptoms of motor weakness, with tenderness on deep pressure over the calf and arm muscles, which were at first attributed to multiple neuritis of alcoholic origin, although the knee-jerks were lively and a slight ankle clonus was present.

This diagnosis seemed to be strengthened by the fact that some of the muscles of the hands became more and more atrophied and that a peculiar eruption occurred on the skin, associated with sweating. Here also the white blood count was quite high, running eventually to about 30,000.

Presently the symptoms took on a distinctly cerebral turn and quite distinct signs of meningitis were developed. A lumbar puncture showed a sterile fluid containing, however, many lymphocytes. Finally the patient developed delusions, although not of the sort usually seen in alcoholic poisoning and eventually had to be sent to a lunatic hospital, where he has remained ever since, free from acute disease, but demented. The temperature was elevated throughout the acute portion of the illness, reaching 103° and 104°.

There seems to be no doubt that one and the same toxic influence may cause various forms of nervous disease, but it is not common to see the different segments of the nervous system successively attacked. For this reason I desire to put on record the case of a man, aged thirty-two years, characterized by the occurrence of a well-marked multiple neuritis of rapid onset, occurring after exposure to a severe wetting and followed, during convalescence, by headache, temporary hemiparesthesia and convulsions, with double vision and high temperature. This seemed, without question, attributable to an encephalitis, and the diagnosis is borne out by the fact that the eventual history of the case showed complete recovery, though the double vision was very slow to pass away.

Finally, I desire to record briefly three cases, apparently of poliomyelitis, in which the onset was remarkably slow and the distribution of motor palsy rather unusual.

The subject of the first of these cases was a child, aged nine years. The first symptom was weakness of the arms, and this was complained of for a day before anything else developed. Then she began to fall down in walking and on the third day she was unable to go up stairs, while on the fourth day she was unable to walk. The subsequent history was that of a case of poliomyelitis, with lesions in multiple form.

The next case is that of a child, aged eleven years. Here there was a progressive onset of motor symptoms, preceded by high temperature (105°) of several days' duration, and since the child had seemed tired and half-sick for two or three weeks before-

hand, it seemed quite possible that this period constituted a prodromal stage. The progressive involvement, first of the legs and then of the arms, seemed to indicate an infection of the Landry type, and yet its occurrence during August and the eventual recovery of the arms seemed to imply a diagnosis of poliomyelitis.

The third case is that of an unmarried women, aged thirty-two years, who had a progressive impairment of the motion of the legs for a month, and during the two following months lost all power in the arms and hands and face and had severe headache and vomiting, although she was at one time unable to move her lips. She had no disturbance of micturition nor of sensibility. The further history of the case recalls Case II. of this series, but, although she improved in many respects, yet, in an examination made fifteen years later, she was found to have a complete toe-drop, a waddling gait, and, what is most remarkable, a typical Argyll-Robertson pupil on both sides. The knee-jerk was absent on the left side, but preserved on the right. No other signs of tabes were present.

SOME UNUSUAL FORMS OF ACUTE MYELITIS.

By B. SACHS, M.D.,

PROFESSOR OF NERVOUS AND MENTAL DISEASES AT THE NEW YORK POLYCLINIC; ALIENIST AND NEUROLOGIST TO BELLEVUE HOSPITAL; NEUROLOGIST TO MOUNT SINAI HOSPITAL.

In this era of bacteriologic research it may seem somewhat hazardous to recur to old-time subjects, but the question of the occurrence of acute myelitis independently of trauma, of specific infection, and of other infectious diseases is one that is still of very great interest. Much confusion has arisen because of the desire on the part of some to apply the term "myelitis" in its strict pathologic sense. Medical purists will be fully justified if they maintain that the term should be restricted to those disease processes that show some tangible sign of inflammation of the spinal-cord substance, and if there were some other term convenient at hand which could be substituted for the word "myelitis" the purists would have things their own way. I can see no harm in giving a more liberal interpretation to this term, for in many instances we have had to depart somewhat from the definition of inflammation that has been in vogue since the days of Cohnheim. For our present purpose, at any rate, let us understand by the term "acute myelitis" a disease process causing a more or less rapid or a more or less complete destruction of the substance of the spinal cord at any given level, excluding, however, those forms which are due to large hemorrhages and to the breaking down of neoplasms. One might speak, in some instances, of myelomalacia or myelonecrosis, but I cannot plead for the general substitution of these terms.

I have been moved to make these few remarks because the first case upon which I wish to report was one in which, from the clinician's point of view, there was every reason to make the diagnosis of an acute transverse myelitis, and yet the autopsy failed to reveal the first sign of any inflammatory process. My special object in

referring to this case is to draw an analogy between the cerebral and spinal vascular accidents of the senile period. We have been hampered for many years in our interpretation of brain and spinal-cord disease by purely anatomic and regional considerations. It is curious that, in spite of the delicate structure of the spinal cord and of its bloodvessels, which is even less favorable than that of the cortex of the brain, the vascular accidents which befall so many persons in advanced years so rarely bring about disease of the spinal medulla. We can understand why embolism should be less frequent than in the cerebral bloodvessels, and even hemorrhage is to be expected less frequently, for the effect of increased blood pressure on spinal vessels is not as great as in the case of the branches of the middle cerebral artery; but there is no reason why thrombosis should not occur in the case of spinal bloodvessels, unless we were to assume that arteriosclerosis and the attendant changes were less common in the bloodvessels of the spinal cord than in those of the brain. The spinal cord of the first patient showed such arteriosclerotic changes, and the affection from which the patient died cannot be interpreted otherwise than a general degeneration of the substance of the spinal cord due to the affected blood supply. It will be well, however, to give the salient features, and those only, of the first case in order to bring out the relative suddenness of onset of the disease and the reason why it was at first suspected that there was nothing but an ordinary acute transverse myelitis or possibly a hemorrhage into the cord:

Professor P., aged sixty-four years, a patient of Drs. Wyeth and Raickstraw, was seen by me in consultation May 5, 1903. He had been well, with the exception of much prostatic trouble, for which a prostatectomy had been done by Dr. Wyeth several months previously. Three weeks prior to May 5th he had been in his home in the South, and, as he stated, "had never felt better in his life." On his return to New York, about one week before my first examination, he was very busy one day driving about a great deal in his endeavor to collect friends for a dinner, and, to quote his words, "I was in a rush generally." Driving about a great deal, he appreciated the fact that there was considerable jolting while in the cab. He stumbled a few times, but paid no attention to it. On the following day, during the act of micturition, he noticed that his knees gave way and he fell to the floor and had to be raised from it. Since that time he has not been able to move his legs and had lost the power of emptying the bladder. There had been slight overflow at times. There was no history of distinct traumatism other than that implied in the jolting of the cab. He had

not been subjected to any drenching and could not account in any way for his sudden disability.

He was entirely clear in mind; speech was normal; pupillary reflexes and all ocular movements were entirely normal. Both the lower extremities were absolutely paralyzed, the toes pointing downward even in the recumbent position. The only movements noticed were involuntary contractions of both lower extremities following upon the slightest sensory stimulation. A careful examination of sensation showed that touch sense was lost below the knees, above the knees touch sense was preserved on both sides, but the pain sense and temperature sense were lost in both lower extremities and extended upward as far as the umbilicus. The knee-jerks were lost; Achilles reflexes also; there was no Babinski phenomenon, and the plantar reflexes were considerably exaggerated. The abdominal and scrotal reflexes were slightly present. The electric examination could not be made at this time, but was hardly needed for diagnostic purposes.

The unusual feature of the case appeared to be the dissociation of sensation above the knees, and thinking that this might possibly be due to central hemorrhage, I was inclined to think the prognosis, as is recorded on my record, a little better than in ordinary transverse myelitis. Two days later, on May 7th, the patient suddenly developed symptoms of intense dyspnœa, and while remaining entirely conscious to the end, died within half an hour after the onset of these symptoms, and before I could respond to the summons which had come to my house.

The *autopsy* was performed thirty hours after death by Dr. Raickstraw, and had, of necessity, to be limited to a removal of the spinal cord, as the family would not consent to a complete autopsy. The entire gray matter in the lumbar region looked pinkish, but arsenic had been injected into the body. There was no other macroscopic change. Above all things particularly noticed was that the gray matter in the dorsal and cervical regions appeared entirely normal, and the substance of the spinal cord was not diffluent at any level. Parts of the spinal cord from every level were submitted to me for examination, and sections from almost every level of the cord were carefully prepared for me by Dr. I. Strauss, to whom I am indebted for a painstaking preparation of these sections. Sections were stained particularly according to the Marchi and Van Gieson methods. The bloodvessels of the cord appeared much distended, but nowhere were there any of the usual signs of active inflammation, nor was there any system degeneration, except that in the upper dorsal and cervical region there was a distinct, probably secondary, degeneration of the posterior columns of the cerebellar tracts and of the anterolateral tracts of Gowers. The Marchi method revealed, particularly in the dorsal and cervical regions, a degeneration of all the white fibers on the circumference of the cord extending partly into the posterior columns, where it was difficult to differentiate between this degeneration of the circumference and the ascending degeneration due to the lesion in

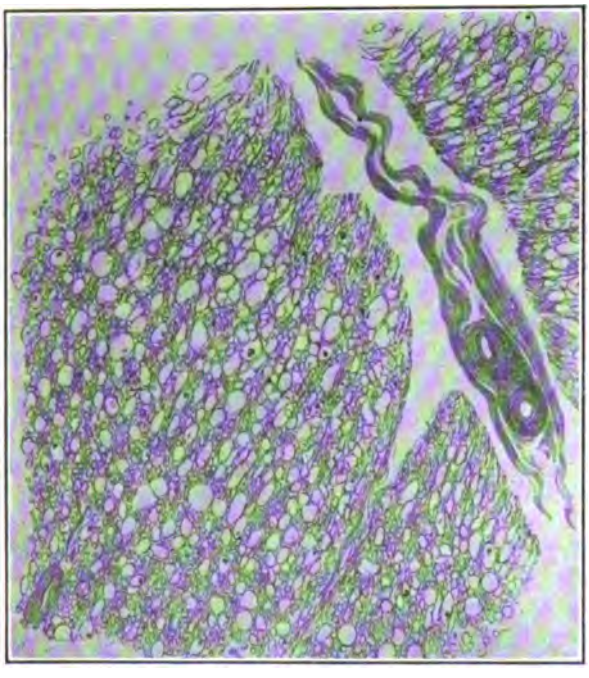
the lower part of the cord. There was not a single sign of central hemorrhage, nor even of punctate hemorrhages in any part of the gray or white matter. The chief changes found were in that part of the cord embraced between the eighth dorsal and the third lumbar segments. Examination of sections from all of these parts presented about the same appearance, and included a distinct degeneration of the cells in the gray matter, as shown in the annexed Fig. 1, and a destruction of the white fibers on the whole cross-section of the cord, without any special reference to the well-known tracts. It will be seen from Fig. 2 that the nerve fibers are distinctly altered, but only a few of them show any distinct axis-

FIG. 1.

cylinders. In the majority of instances homogeneous masses indicate the presence of the white fibers; bloodvessels on the cross-section of the cord are hypertrophied; many of them are occluded. In many instances the larger vessels entering the cord are completely blocked with blood, and the clots are partly organized, but there is no sign anywhere of any active inflammatory process. Of the bloodvessels of the pia it may be said that they exhibit a general thickening of the walls, particularly of the intima, and the changes are such as might be attributed to a general arteriosclerosis and are entirely distinct from such changes as we observe with specific endarteritis.

This case admits of no other interpretation than that of an ischæmic necrosis due to a general arteriosclerosis. The entire absence of inflammatory conditions would seem to put the case into a different category from the ordinary acute transverse myelitis, as it occurs in younger individuals. The partial dissociated sensation which occurred, which was so pronounced a symptom of the condition, and which ordinarily points to change in the central gray matter and as a rule to hemorrhage in this region or to cavity forma-

FIG. 2.



tion, was evidently due to the decay of the nerve fibers in the posterior columns adjoining the central gray matter and to the involvement of part of this gray matter itself. The extension of the process upward and the involvement of the cervical portion of the cord must be held responsible for the death due to respiratory paralysis. We have been accustomed to extend the term "cerebral apoplexy" to all of the vascular accidents occurring in the brain during the senile period, and do not restrict it merely to cases of cerebral hemorrhage.

One is strongly tempted, therefore, to speak of a case such as the present one as one of spinal apoplexy, even though every sign of hemorrhage were wanting. But spinal apoplexy has at all times been restricted to actual hemorrhage into the cord, and for that reason the term is not altogether applicable. But the point that I wish to enforce is, that one must infer that one of the conditions which, when it affects the bloodvessels of the brain, gives rise to cerebral apoplexy, has in this instance caused a spinal affection. But the wonder is that such conditions are not met with more frequently, since the blood supply of the posterior half of the spinal cord with its slender posterior and posterolateral bloodvessels, as has been abundantly shown by the researches of Williamson and others, is far less favorable than is the blood supply of the greater part of the brain. These acute spinal paralyses in the senile period, leading to fatal issue, are unquestionably rare, but it is only fair to suspect that many of the lesser and more chronic spastic paraplegias of the same period may be due to the arteriosclerotic changes in the bloodvessels of the cord. At all events, it appears to me that it will be well worth while to examine similar cases most carefully, and to pay more attention than has been the case hitherto to spinal vascular accidents occurring in the adult at the age of fifty and later.

In marked contrast to the case just related is the second case of a young girl of fifteen who was admitted into Mount Sinai Hospital November 10, 1902. The family history of the patient was negative, and the patient herself had passed through none of the diseases of childhood except measles.

Four days before the patient was admitted into the hospital she had returned one evening from her day's work and had complained of lancinating pains in both sides of the trunk and radiating toward the median line of the abdomen; a feeling of heaviness and numbness in both feet. Five minutes later, according to her story, she became unconscious, but did not fall from the chair. The unconsciousness lasted fifteen minutes, but there were no convulsions. As soon as she regained her senses she noticed that there had been involuntary urination and the power and feeling in the lower extremities were completely gone from the toes upward as far as the groins. As evidence of the loss of sensation, we found marked burning of the skin, from the hot-water bottles that had been applied in her home. At the first onset she had not complained of pain or of any paræsthesia, but there was complete retention of urine and constipation. She referred to a constant "dull, boring" sensation in the lower dorsal and upper lumbar spines. There was no girdle sensation and both power and sen-

sation in the arms were entirely normal. At home she had repeated severe chills and high fever. According to the physician's statement temperature varied between 100° and 103°.

When she was admitted into the hospital the first examination of the urine proved that it was already ammoniacal. The first examination at the hospital also revealed a swelling on the right buttock, and a black necrotic area on the left leg just above the ankle on the inner side; on both great toes and on the small toes were a number of blebs. There was a very large bleb, 5 x 4 inches, on the left heel, and a few blebs on the right foot. There was no atrophy of the lower limbs, but both lower extremities were absolutely paralyzed. Passive movements could be easily carried out and caused pains in the vicinity of the lumbar spine. There was retention of urine, and involuntary defecation. The patellar reflexes were absent; there was no Kernig sign and no Babinski.

Electric examination of the lower extremities showed good response to galvanism, using a strong current, but faradic response was entirely lost. There was a general impairment of all forms of sensation to within one centimeter of the umbilicus. From the day of admission to November 22d, a period of twelve days, the patient ran temperatures varying between 102° and 105°. During this time a very large, subcutaneous abscess appeared over the left gluteal region, which was incised and drained under the guidance of Dr. Lilienthal, who stated distinctly, however, that there was no connection between the abscess and the vertebral column.

The bacteriologic examination of the pus from this abscess showed that it contained streptococci. At this same time, and for weeks following it, abscesses appeared over the calves, over the outer surfaces of the thigh, and on various parts of the lower extremities. The patient was removed to the surgical ward and was under continual treatment for these abscesses for many months. To add to the girl's misfortunes she developed erysipelas in March, 1903, and for a time was transferred to the isolation house and another similar experience necessitated her removal again in July of this same year. The various abscesses ultimately healed, and in spite of the development of innumerable complications from these multiple abscesses and from the cystitis, the girl's general health improved, and in the autumn of 1903 she gradually regained some power over the thigh muscles, being able slightly to pull the legs upward, and was even able, in November and December, 1903, to move the legs so that she could take a few steps when supported under the arms by competent nurses. On January 8, 1904, she was transferred to the Montefiore Home, where I was again permitted to see her some ten days ago.

At the present time her general condition shows marked emaciation, her power over the legs has not increased; she presents many scars due to the incision of the various abscesses, but there has been a very marked recovery in sensation, so that the anterior and inner aspects of the thigh have regained much of their sensory power. From all present indications the girl will remain more

or less paralyzed and more or less anesthetic in the lower extremities. She will not be likely to regain much power over the vesical reflex, and for the rest of her days will in all probability be either chairridden or bedridden.

While there is no pathologic examination in this case to substantiate any theories that may be held regarding it, the case was most unusual because of the remarkable suddenness of the onset, such as we are accustomed to associate with hemorrhage into the cord. The simultaneous development of the spinal-cord affection and of the multiple abscesses would leave very little doubt as to the septic character of the myelitis. At the beginning of the disease there was some hesitancy on my part in the interpretation of the symptoms, for the first large gluteal abscess that appeared suggested the probability of vertebral caries, although the suddenness of the onset, in view of the preceding perfect health, militated somewhat against this diagnosis. When the surgeon, however, reported that there was no connection between the abscess of the vertebral column, the idea of caries had to be abandoned and the rapid appearance of abscesses all over the lower extremities convinced me that there was good reason to regard the myelitis as the expression of a streptococcic infection of the spinal cord. The younger men on the House Staff of the hospital would not appreciate my reasons for not consenting to a lumbar puncture, by means of which the septic character of the myelitis would have been proven; but I was not willing to risk the danger of a purulent meningitis as the result of such puncture, and, if I failed to corroborate the suspicions I entertained, there is at least some satisfaction in knowing that the girl escaped a septic meningomyelitis which would unquestionably have proved rapidly fatal, and which would have been wellnigh unavoidable in view of the multiple abscesses in the skin and subjacent tissues.

Various French observers, notably Charrin, Grancher, Martin, Manfredi et Travers, Widal and Besançon have produced foci of degeneration in the spinal cord by the injection of various microbes and of their toxins. Marinesco has obtained very positive results by injecting streptococci and other microbes into the arachnoid cavity. A number of cases of septic myelitis in man have been reported, but the evidence is not entirely satisfactory. Although the evidence is circumstantial in this instance, I believe there is a strong reason to suppose that this was a case of streptococcic myelitis from which recovery had been at least unusual, but by no means complete.

Both cases referred to in this paper are recorded merely for the purpose of insisting that the spinal cord, well protected and exempt as it is from many of the accidents which befall the brain much more frequently, does at times become the seat of similar morbid processes, and that it will not do to restrict the term myelitis merely to the morbid process that can be distinctly traced to trauma, syphilis and to the ordinary acute infectious diseases.

DISCUSSION.

DR. PARK: I was rather startled by Dr. Sachs saying that the lumbar puncture if carried out here would have caused a septic meningitis. I would like to ask if he has had any experience that caused him to come to that conclusion?

DR. WELCH: I was very much interested in Dr. Sachs' cases because, as he said, many of them appear in the literature as septic myelitis, and, as he has also said, the spinal cord is very sensitive. If you compress the abdominal aorta of the rabbit for an hour it is followed by a myelitis, because the cord is so very sensitive to anemia. Anatomically many of the cases are not true inflammations of the cord, but it would be inconvenient to withdraw the name of myelitis from these cases at present.

DR. JACOBI: Is not this the result of the different structure of the blood-vessels of the spinal cord from those of the rest of the body? The muscular layer is absent, and would not that explain why the circulation is more readily interfered with in the spinal cord than in any other organ?

DR. SACHS: I tried to make the point that it is remarkable that the blood-vessels of the spinal cord are interfered with so little. I am very glad indeed to hear Dr. Welch's remarks about the analogy of the findings to those of experimental work. I was at a loss to explain these conditions except by comparing them with animal experimentation.

With regard to Dr. Park's remarks, I think we ought to understand our position very fully there. Those who have done lumbar puncture know that it is a very easy matter to get into the spinal canal, but in order to withdraw the fluid you must get between the spinal cord and the dura, and one would hardly be willing to assert that in a case with multiple streptococcic abscesses he would not run the risk of infecting the membranes. You may have a focus of sepsis in the cord which is destructive at that point, but it is an innocent affair compared with an infection of the cerebrospinal canal. Hence we must avoid the risk of introducing any of this septic substance into the general spinal canal.

A CASE OF ENTERIC FEVER COMPLICATED BY POLYURIA.

By J. C. WILSON, M.D.,
of Philadelphia.

The moderate polyuria which often attends the period of defervescence and early convalescence in the acute febrile infections is too well known to excite comment, and the literature abounds in instances of glycosuria as a complication of these diseases. But transient non-saccharine polyuria, at one time exceeding, as in the following case, 6000 c.c. in twenty-four hours, developing in the course of an attack of enteric fever and subsiding with the decline of the temperature, must be very rare. I have never before had the opportunity of observing such a case, and such examination of the literature as I have had made fails to discover analogous cases. Very recently, I learn that my friend Dr. Fussell has observed a similar case, which he will report on this occasion. For nosologic purposes it would be well if the distinction between polyuria as a symptomatic and transient condition and diabetes insipidus as a substantive affection, a distinction corresponding to that between glycosuria and diabetes mellitus, were more generally observed.

Enteric fever with prolonged and peculiar delirium in a male adult, complicated by massive polyuria developing in the midcourse of the attack and subsiding with the fall of the temperature. Treatment, systematic cold bathing. (Notes by Dr. Kalteyer.)

REPORT OF CASE.

J. W. V., aged twenty-nine years, single; birthplace, Michigan; occupation physician. Admitted to the medical ward of the Jefferson Hospital September 25, 1902.

Diagnosis. Enteric fever complicated with polyuria.

Family History. Father, mother, two brothers and one sister living and in good health. There is no history of neuropathic, cardiac or tuberculous disease in the family. The patient's mother suffered from cancer of the breast which, three years ago, was successfully removed by operation and has shown no signs of recurrence.

Previous Personal History. The patient was informed that he had measles and chicken-pox in early childhood. At the age of six years he suffered from diphtheria. Some years ago he had an attack of catarrhal jaundice which lasted for about ten days. At twenty-six years he suffered from an acute illness of about a week's duration, which was said to be acute appendicitis, the principal symptoms of which were colicky abdominal pains, at first general and later localizing itself in the right lower abdominal quadrant, vomiting and fever. He made an uneventful recovery without operation and so far has not had a relapse. After this illness he enjoyed good health until the present illness. He has never suffered from Neisser's disease or syphilis; he has used alcohol moderately and smoked occasionally.

History of Present Illness. Four days prior to his admission into the Jefferson Medical College Hospital he complained of loss of appetite, malaise and severe frontal headache. The patient states definitely that previous to September 21st (four days before entrance into the hospital) he appeared to be in excellent health; his duties, which consisted of an obstetric practice in Philadelphia, made great demands upon his time. During the past summer he was in the habit of drinking unfiltered and unboiled water. On Monday morning, September 22d, his condition had somewhat improved; he had slight browache, although soreness in the muscles of his limbs was a prominent symptom and his appetite remained impaired. On Monday evening his temperature registered 99⅖°, headache grew worse, and, becoming somewhat anxious about his condition, he took 1½ grains of calomel in divided doses. On Tuesday morning he had a loose bowel movement; his temperature registered 99°; headache was now constant and distressing and weakness pronounced. In the evening his temperature registered 101⅖°. On Wednesday morning the temperature was 101°, his condition was decidedly worse, and in the evening the temperature rose to 103°; during the course of the day the symptoms previously mentioned intensified. He took to his bed on Thursday morning, when he was admitted to the hospital.

Condition on Admission. Temperature, 101.2° (axillary); pulse rate, 90; respiratory rate, 20; cheeks flushed; pupils dilated and the tongue coated lightly on its dorsum with a whitish fur. The abdomen was somewhat tympanitic; the spleen could not be palpated, but on percussion evidence of enlargement was noted. The heart and lungs appeared normal.

Blood examination revealed the following: erythrocytes, 4,580,000 per cubic mm.; leukocytes, 8600 per cubic mm.; hemoglobin, 80 per cent.; color index, 0.88.

The blood gave a positive agglutination reaction with the bacillus typhosus. The urine did not give Ehrlich's diazo reaction.

On September 27th, two days after admission, a single rose spot, which disappeared on pressure and reappeared when pressure was released, was discovered in the epigastric region.

The treatment ordered on admission was as follows: Liquid diet—milk, broths, etc., at three-hour intervals; one grain of calomel in divided doses. Sponging with water having a temperature of 60° when his axillary temperature rose as high as 102° and tubbing in water at 70° when his temperature registered 103° or higher every three hours. During the plunge a half-drachm of aromatic spirit of ammonia was administered. At intervals of six hours a Leiter coil was applied over the heart, through which hot water was passed for about a minute and then cold water for about twenty minutes. On October 1st, when Professor Wilson took charge of the service, the treatment was modified. The diet was unchanged, but other measures were discontinued, and bathing in water having a temperature of 70° was ordered every third hour when the temperature in the axilla registered 101.5°. The patient was given one-half ounce of whiskey during and after the plunge.

The disease seemed to run a typical course, except that delirium of a low, wandering type, later becoming very active, manifested itself early and was quite constant, abating only after the plunges, when as a rule the mind remained clear for a short time. Crops of rose spots were observed from time to time.

The lower edge of the spleen was palpable during the second week. The pupils remained dilated; the tongue became very dry and its coating was thick and brown. He often complained of dryness in the mouth. Constipation prevailed during the entire course of the illness, being especially pronounced in convalescence. Enemata were given at regular intervals. Emaciation set in rapidly. The quantity of urine began to increase on October 5th and urination became frequent. The highest amount voided was 215 ounces on October 16th. The patient suffered from an unquenchable thirst. He was constantly craving water, which was given to him in liberal amounts. The delirium became more severe during the third week, when a peculiar wandering of mind was present. He frequently complained of thirst and became difficult to manage.

His mental agitation was accompanied by considerable restlessness. As a rule, the delirium conformed to an active type and the patient often engaged in conversation with those about him. He was in the habit of discussing various medical topics incoherently and his thoughts seemed to dwell upon his condition. The mental derangement continued into convalescence and subsided very gradually. Subsidence of the polyuria was also gradual. On October 16th valerianate of zinc in one-grain doses and ergotin in three-grain doses were administered three times per day. After he had fully regained consciousness he remarked that he recalled but few events of his illness, except that his mind was

often clear during and for a short time after the plunge. Polyuria was a most conspicuous sign, and while this was most marked micturition was so frequent that it was necessary for the patient constantly to have a urinal either upon his bed or upon the table adjoining it.

The accompanying chart shows the daily variations in the amount of urine during the course of the illness:

Urine Examination, September 27, 1902. The quantity of urine for the twenty-four hours preceding was 30 ounces. Color, amber; transparency, clear; specific gravity, 1.018; reaction, acid; albumin, a faint trace present; sugar, not present; urea, 2.1 per cent.

Microscopic Examination. Amorphous urates, squamous epithelial cells and a few granular casts were found.

Urine Examination, October 8, 1902. The quantity of urine for the twenty-four hours preceding was 55 ounces. Color, straw-colored; transparency, clear; specific gravity, 1.003; reaction, acid; albumin, a faint trace present; sugar, not present; urea, 0.7 per cent.

Microscopic Examination. Amorphous urates and squamous epithelial cells were found.

Urine Examination, October 11, 1902. The quantity of urine for the twenty-four hours preceding was 80 ounces. Color, straw-colored; transparency, clear; specific gravity, 1.004; reaction, acid; albumin, a faint trace present; sugar, not present; urea, 0.8 per cent.

Microscopic Examination. Amorphous urates and squamous epithelial cells were found.

Urine Examination, October 16, 1902. The quantity of urine for the twenty-four hours preceding was 215 ounces. Color, straw-colored; transparency, clear; specific gravity, 1.005; reaction, acid; albumin, a faint trace present; sugar, not present; urea, 0.6 per cent.

Microscopic Examination. Amorphous urates and a few squamous epithelial cells were found.

Urine Examination, October 18, 1902. The quantity of urine for the twenty-four hours preceding was 130 ounces. Color, light straw color; transparency, clear; specific gravity, 1.001; reaction, faintly acid; albumin, a faint trace present; sugar, not present; urea, 3 per cent.

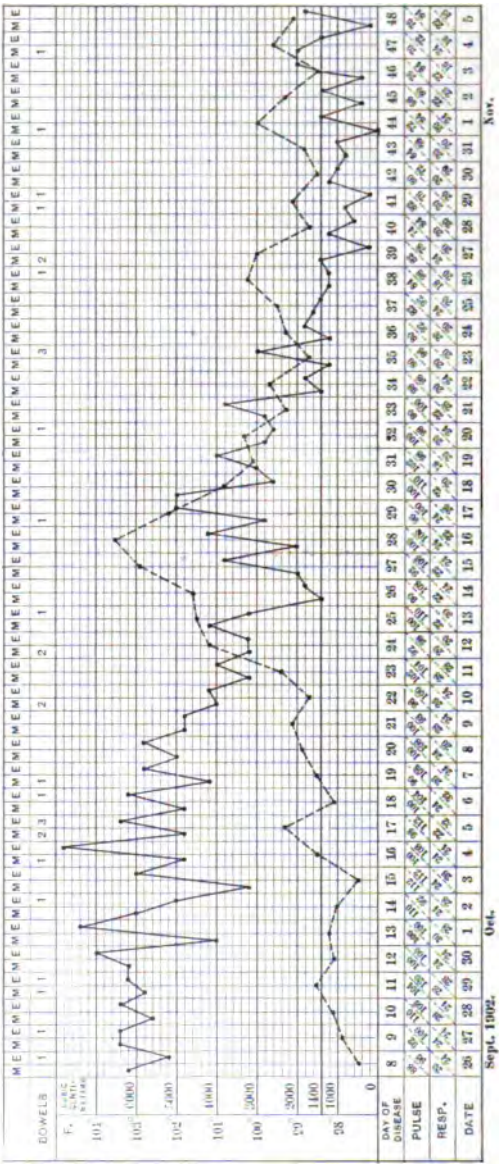
Microscopic Examination. Amorphous phosphates and a few pus cells were found.

Urine Examination, November 17, 1902. The quantity of urine for the twenty-four hours preceding was 40 ounces. Color, amber; transparency, clear; specific gravity, 1.015; reaction, acid; albumin, not present; sugar, not present; urea, 1 per cent.

Microscopic Examination. Amorphous urates, a few epithelial cells, and a few pus cells were found.

The total amount of urea for periods of twenty-four hours, at the height of

the polyuria, was increased and the accompanying chart illustrates the variations in the total amount.



Convalescence was uninterrupted and uneventful. The patient was given a soft diet after his temperature had remained normal for seven days.

He was discharged from the hospital on November 25, 1902, and has remained well until the last report, about the close of the year 1903.

After the polyuria had reached an amount which excited our special interest a daily record of the quantity of fluid ingested was kept. It is a matter of regret that this document, which properly forms part of the history of this case, has been mislaid. The polydipsia was as marked as the polyuria, and no restriction was placed upon the amount of water given the patient except that no single draught should exceed two ounces, it having been found that the craving recurred as quickly after larger quantities.

I have no hypothesis to offer as to the significance of the polyuria in this case. It was evidently the cause, not the effect, of the great intake of fluid; the patient was neurotic and overworked, but did not present the symptoms of any organic disease of the brain or nervous system. It cannot, in view of this enormous number of cases of enteric fever that have now been treated by systematic cold bathing, be ascribed to that measure, since many accurate studies of the urine have shown a very constant moderate increase, but no such enormous output as in the foregoing case.

CLINICAL STUDIES IN ARTERIOSCLEROSIS.

By ALFRED STENGEL, M.D.,
PROFESSOR OF CLINICAL MEDICINE, UNIVERSITY OF PENNSYLVANIA.

ARTERIOSCLEROSIS is a pathologic condition of such extent and presents itself under so many guises that it would be impossible to present the clinical features in the compass of a paper of ordinary length. It is not, therefore, my purpose to discuss the symptoms fully, but only to touch upon some of those which have impressed themselves upon my mind as important in diagnosis. With regard to the latter I am more interested in the early recognition of the disease than in the diagnosis made when secondary alterations have occurred in various organs of the body. It is no doubt true that much may be accomplished by treatment even in the late stages and a recognition of the disease at any period is desirable. If, however, the process is to be arrested or cured, the initial manifestations must be recognized.

My clinical studies have impressed upon me the belief that there is a wide divergence in the nature of arteriosclerosis developed in the presenile period as a result of more or less well-recognized causes and that which occurs during true senile involution. I cannot enter at length upon this phase of the subject now, as it does not, strictly speaking, belong to the clinical side of the question; but I will add only that my conception of the senile form of disease is one of a process that is essentially diffuse and, perhaps, involves the extravascular tissues simultaneously with the vascular apparatus, while the presenile form or pathologic arteriosclerosis is in the beginning a disease of the bloodvessels alone. There seems also to be some difference in the character and distribution of the lesions. Possibly as a result of this restricted involvement of the vessels and the character of the lesions, degen-

erative changes in the organs are much more rapid of evolution than in the senile type of arteriosclerosis, and a rapid clinical course is more likely to occur. Clinicians will readily recall cases in which the symptoms appeared abruptly after some shock or strain, mental or physical, and in which the whole clinical course was that of a severe, even a malignant, process. Indeed, I have known such cases to be mistaken for obscure carcinoma until the autopsy disclosed the real nature of the disease and the absence of cancer.

Among the clinical conditions to which I wish to call attention are the alterations in the blood, the changes in the character of the urine, the condition of the skin and the cardiovascular phenomena.

With regard to the conditions of the blood, I have long been impressed with the importance of recognizing the existence of a spurious anemia in arteriosclerosis and have in several places discussed this symptom. In the later stages of the senile form, and to a less extent in the pathologic or presenile type, the patient's color becomes an ashy white that suggests cachexia or at least a high grade of anemia; yet in these cases examination of the blood shows no commensurate reduction in the number of corpuscles or the coloring matter.

The following figures give a clear idea of the disproportion between the character of the blood and the apparent anemia. These patients were all decidedly pallid and some were supposed to be very anemic until the blood examination revealed the true condition:

	Hemoglobin.	Erythrocytes.	Leukocytes.
1. J. M. S.	82 per cent.	.....	.....
2. M. R.	90 "	.....	8,650
3. B. R.	88 "	5,340,000	10,000
4. C. L. P.	80 "	4,960,000	7,950
5. W. J. C.	85 "	5,280,000	5,700
6. S. N.	90 "	5,030,000	.....
7. W. H. I.	80 "	.....	.....
8. C. A. G.	90 "	4,820,000	8,342
9. C. A. C.	85 "	.....	.....
10. C. B.	90 "	5,030,000	8,624
11. D. B.	95 "	.....	.....
12. C. D. B.	90 "	4,320,000	12,000
13. A. G.	85 "	6,060,000	9,920
14. J. H.	77 "	5,300,000	12,000
15. McT.	79 "	4,490,000	9,240
16. R. E.	73 "	5,100,000	8,000
17. A. K.	83 "	5,690,000	9,760
18. Dr. H. B. R.	88 "	5,340,000	10,048
19. Mrs. B.	75 "	4,680,000	8,150

Most of the cases included in the above table were fairly advanced at the time of the examination. I have found, however, that pallor without corresponding anemia is sufficiently striking, even in the earlier stages of the disease, to constitute a combination of conditions of some value in diagnosis.

The explanation of this condition would form an interesting study. I have always believed that the cause lies in contracted vascular channels which occasions the pallid appearance, though it does not affect the constitution of the blood. An analogy is found in the early anemia of persons who have recently taken up their residence in tropical countries and in whom pallor without corresponding anemia is frequently encountered. Very similarly some cases of spurious anemia developed as a result of nervous influences have been reported.

The condition of the urine in arteriosclerosis is by no means a uniform one at any stage of the disease and presents no positive criteria for diagnosis. Nevertheless there are certain peculiarities that are sometimes suggestive. Among other changes I have been struck with the tendency to variability in the specific gravity and in the quantity without reference to the quantity of liquid consumed. A wide variability in the specific gravity between the morning and evening specimen has been particularly striking in some cases and seems to me to be met with in a considerable proportion of the cases during the earlier stages. The amount of water in the urine is so distinctly dependent upon vascular conditions that it does not seem surprising to find great fluctuations in a condition in which some alteration of the small bloodvessels and capillaries may be assumed to be present. My own view inclines strongly to the recognition of capillary lesions in the early period of arteriosclerosis, and if such were present marked fluctuations could readily occur in the excretion of water. These fluctuations in the specific gravity frequently antedate the first appearance of a slight trace of albumin which sooner or later gives evidence of the existence of renal change. The following table taken from some recent cases of early and late arterial disease is instructive :

	Urine.	
1. W. P. W.	M. 1016 E. 1034	Traces of albumin at times.
2. J. S. Worth	M. 1014 E. 1024	Traces of albumin at times.
3. Dr. H. R.	M. 1018 E. 1030	Faint trace; few hyaline casts.
4. W. J. O.	M. 1020 E. 1026	Trace at time; hyaline casts.
5. S. A. K..	M. 1008 E. 1024	Trace at times; no casts; few red blood corpuscles.
6. B. F. C..	M. 1018 E. 1030	Trace at times.
7. J. W. C..	M. 1016 E. 1024	Occasional trace.

Glycosuria is met with sufficiently often in arteriosclerosis to be regarded as a possible consequence of that condition. My observations seem to indicate that it occurs in the middle period of the disease, and disappears later, though sometimes it is met with quite early. There is a marked contrast in the frequency of occurrence of this symptom between the presenile and the senile form of arteriosclerosis. In the latter type I have much more rarely met with transient or recurring glycosuria.

The behavior of the sweat-glands is somewhat similar to that of the kidneys. A tendency to paroxysmal sweating of marked character occurs in a considerable proportion of the cases and is almost exclusively a symptom of the earlier period. At the same time in the disease a slight puffiness or edema occurs in some instances. These conditions are scarcely marked enough to be of much value in diagnosis, but it is important to recognize their occurrence as consequences of simple arteriosclerosis because they are so frequently attributed to other and, perhaps, graver conditions.

CARDIOVASCULAR CONDITIONS. Particular interest centers in the study of the circulatory phenomena and especially in the study of the blood pressure. The direct examination of the pulse with the finger enables the clinician to determine roughly the state of the arterial pressure and until recently no more accurate means were available. The sphygmograph had, indeed, been used and with some success by those especially skilled in its employment, but was generally discredited, though I believe without sufficient justification. Properly used this instrument is a valuable aid

in the study of the blood pressure. Other forms of apparatus, however, have superseded it and give more reliable information regarding the pressure. These instruments give two distinct sorts of data. The von Basch sphygmomanometer and similar instruments record the maximum or systolic pressure; the Hill and Barnard apparatus indicates the diastolic pressure. None of the earlier methods recorded both systolic and diastolic pressure, and in consequence their value in the study of peripheral circulatory conditions is comparatively small. Gumprecht, von Recklinghausen and T. Janeway devised modifications of the old methods by which both systolic and diastolic pressure may be determined, and my associate, Dr. Stanton, has constructed an apparatus which is more satisfactory for clinical purposes than any other now available. It needs little discussion to prove that the single determination of either systolic (Riva-Rocci, Gärtner) or diastolic pressure (Hill and Barnard) is comparatively valueless. Neither gives a correct estimate of the actual condition of the circulation or of the mean pressure.

A record of the high and low pressure more accurately indicates the probable mean pressure, though, of course, it does not permit of a positive determination of the mean, since the duration of the high and low point would determine the relative value of the figures in estimating the mean. However, a knowledge of the systolic and diastolic pressure indicates approximately the general condition of the circulation.

Much has been written about the blood pressure in arteriosclerosis and in senility. German authorities following von Basch look upon continued high pressure as an evidence of established arteriosclerosis; while, on the other hand, certain English writers, notably Allbutt, believe there is a presclerotic stage of arteriosclerosis in which occasional or continued high pressure is produced by increased viscosity of the blood or by irritative spasm of the arterioles.

The whole work of determining the relation of blood pressure to arteriosclerosis needs thorough revision. In view of what I have said about the determinations of high, low and mean pressure, records of systolic pressure are significant mainly of

the capacity of the left ventricle while diastolic pressure indicates the degree of perpheral resistance and the elasticity of the larger vessels. The combination may be helpful in determining the circulatory conditions both at the center and the periphery.

My own observations in determining the pressure in established arteriosclerosis have shown a retained pressure between the systoles, that is to say, a comparatively high diastolic pressure. The following figures selected from many observations will indicate my point:

C. A. G.	systolic	150	diastolic	105
J. C.	"	150	"	100
J. C. W.	"	195	"	155
C. H. T. (1)	"	125	"	85
" (2)	"	105	"	75
" (3)	"	100	"	87

I have selected these records out of others for the reason that they indicate the conditions of pressure when the systolic pressure is high as well as when it is low. In the case of C. H. T. it will be observed that the systolic pressure was consistently low, but the diastolic pressure was comparatively maintained, or, to state it in another way, the diastolic pressure was relatively excessive. This case was one of well-marked general arteriosclerosis. The average pressures obtained with the instrument I have employed are for adults, about 140 to 160 systolic and 75 to 85 diastolic. In conditions in which the blood pressure becomes generally depressed both the systolic and diastolic pressure sink. It will be observed in the figures of the case of C. H. T. that the systolic pressure did fall, but the diastolic pressure remained fairly established. This observation is in entire accord with pathologic knowledge of the location of the principal changes in arteriosclerosis. The smaller bloodvessels, arterioles and probably capillaries are the principal seat of change, and in consequence so long as the aorta and the larger vessels retain a certain degree of elasticity, which I believe is true up to a very late stage in the disease, so long will the diastolic pressure be sustained. If the elasticity of the large vessels were wholly destroyed the diastolic pressure would fall to a minimum.

The instrumental estimation of the blood pressure will be seen

to possess special advantages for the reason that it permits of a determination of sustained arterial tone when the mean pressure is unquestionably reduced to the point which makes accurate determinations with the palpating finger impossible.

AUSCULTATORY PHENOMENA. I wish to allude very briefly to an auscultatory condition that appears to me of essential importance in the earlier stages of arteriosclerosis, namely, the peculiar prolongation of the first heart sound. Just as in aortic stenosis, in which the resistance to the outflow of blood is close at hand, the heart's systole becomes slow and labored, so in arteriosclerosis to a less degree a prolonged systole is the rule. This is determined with some accuracy by the character of the first heart sound. It contrasts sharply with the peculiar slapping sound of the later stages of the disease when the left ventricle has become overtaxed and has dilated. I cannot better describe the character of the sounds I have in mind than to say that it resembles that which results from the too energetic administration of digitalis. Murmurs and accentuation of the second sound of the heart are later and less important phenomena, though perhaps more certainly indicative. This, however, is true of all the symptoms; the early signs are uncertain ones, though on careful study they give some indication of the beginnings of the disease.

DISCUSSION.

DR. KINNICUTT: Has Dr. Stengel observed the low blood pressures mentioned by him in cases of senile arteriosclerosis, or in what Dr. Stengel has termed pathologic arteriosclerosis? My own observations have been that the blood pressure in senile arteriosclerosis is rather lower than in the so-called pathologic sclerosis.

DR. COHEN: There are so many factors involved in the estimation of blood pressure that it is difficult to say just what element has the greatest effect upon the pressure as observed with the finger or instrumentally. It is only the net result that we can express mathematically, and whether the change noted be due to change in the structure of the arterial wall or change in innervation or alteration in the force with which the blood is sent out from the ventricle, the mathematic

results will not tell us. I consider it unfortunate that in our clinical and physiologic observations we should follow the engineering plan of looking upon blood pressure and arterial tension as synonymous terms. The arteries are not passive tubes, as in artificial constructions, but active, contractile agents. I should prefer to speak of the ventricular impulse as "blood pressure," and by "arterial tension" indicate the tonus of the vessel.

The old clinical observation of Broadbent, which applies of course to more advanced pathologic conditions than Dr. Stengel has referred to, namely, that the fulness of the artery "between beats" rather than during the beat is to be watched for evidence of arterial change, goes hand-in-hand with Dr. Stengel's observation as to sustained diastolic pressure measured in the tonometer. In my own observations I have been inclined to lay much stress not only upon the prolongation of the first sound as reported in the paper, but also upon its impurity. Looking over my notes I have been impressed with the frequency of this record, "impurity of the first sound," indicating a faulty action of the heart rather than a structural, valvular or orificial, lesion sufficient to produce distinct leakage.

The point in regard to the urine should, I think, be pushed a little farther. I have found not only changes in the specific gravity but in the toxic coefficient, and I think there is a tendency in many cases to variation in the excretion of the toxic elements. I speak of this not from tests of toxicity upon animals, but from chemical studies of the urine of patients and from their symptoms. Whether or not the condition is due to a loss of liver function dependent upon early cirrhosis, or, if you choose, a "pre-cirrhotic stage," is a subject well worth further clinical and laboratory study.

DR. STENGEL: In answer to the question I would like to say that the cases of low pressure to which I referred were not senile, but rather cases of pathologic arteriosclerosis

THE HEART AND CIRCULATION IN PREGNANCY AND THE PUERPERIUM.[1]

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It was asserted by Larcher that the heart becomes hypertrophied during pregnancy. This view has generally been adopted by French writers and opposed by most German authors following Gerhardt. A study of the matter seemed to us of interest on its own account, as well as for the light it might throw on the conditions that may determine hypertrophy.

1. The Vascular System in Woman. There are certain differences in the circulatory system of women as compared to that of man that require consideration before the effects of pregnancy can be properly estimated. In general, the statement may be truthfully made that the heart is smaller, its walls somewhat thinner and its power less in the adult woman than in the adult man. The bloodvessels are probably of less caliber, even allowing for the differences in size and weight; so that the vessels in a man would be on the average of greater caliber than those of a woman of equal weight. This assertion cannot be positively proved, but is at least likely when the greater frequency in women of positive

[1] Read in abstract at the meeting held at Washington, May 13, 1908.

hypoplasia of the heart and vessels is kept in mind. The comparative narrowness of the vessels is, perhaps, in keeping with the higher proportion of adipose and lower proportion of muscular tissue in woman. Further, it is probable that the elasticity of the vessels is greater. The effects of these differences on the circulation are of opposite character. The smaller size and lesser power of the heart would in themselves tend to lower pressure, while the narrower channels of circulation would act in the opposite direction and the greater elasticity of the vessels would, on the contrary, dispose to lower blood pressure. The resulting degree of pressure must depend upon the value of the conflicting influences. This can be determined by actual measurement with some form of apparatus by which peripheral blood pressure can be estimated. Reference will be made to the scanty observations that have been published and our own determinations in pregnant and parturient women will be detailed. It may be said here that the pressure is uniformly lower in woman and clinical observation sustains the view that from every aspect the circulation of woman may be regarded as less active than that of man.

2. The Effect of Work on the Heart and Circulation. This question requires preliminary consideration, because it has very frequently entered into discussions of the effects of pregnancy on the heart. Laborious occupations have long been recognized as causes of hypertrophy of the heart and of arteriosclerosis. The effect of less protracted muscular exertion is not so uniform or certain. The normal heart is possessed of a considerable degree of reserve power, which enables it to maintain the circulation during physical strains of considerable magnitude without suffering change. When, however, the heart is subjected to excessive strain it is liable to dilatation in proportion to the degree of the labor imposed and the inefficiency of the heart muscles to meet the demand. In athletic exercises or any temporary occupation involving similar exertion the right heart suffers to a greater degree than the left, doubtless as a result of its relative weakness and of the comparatively greater labor imposed upon it by the acute emphysema of the lungs and consequent compression of the terminals of the pulmonary artery. Soon, however, the heart regains its equilibrium of action, if the exertion is not excessive; but in certain cases

such recovery does not follow and the phenomena of acute dilatation of the heart are observed, as in mountain climbers, athletes or the like.

Between these extremes of chronic muscular overexertion (laborious occupations) and acute excess of labor (mountain climbing, etc.) are various grades of strain that may or may not affect the heart in accordance with the strength of that organ and the degree of work imposed. Without entering into details about any other of such conditions, we may proceed to a consideration of pregnancy as one that has been supposed to increase the work of the heart sufficiently to cause hypertrophy of its walls. Among the factors supposed to contribute to increased work of the heart in pregnancy are the following: increase in the number and size of the vascular channels (uterine, placental, etc.), increased quantity of blood (plethora of pregnancy), increased intra-abdominal pressure due to the growing uterus, insufficient expansion of the thorax and compression of the lungs. Opinions vary as to the existence and significance of these factors of supposed increase of cardiac work. There is undoubtedly an increase in the size and the number of vascular channels in the uterus, the effect of which, independent of other conditions, must be an increased area of internal friction and consequently increased work. Fellner, quoting Lahs, states that there is a decrease of work involved in increased channels when the influx and outlet are unaltered, even when there is a considerable numerical increase in channels. The truth of this statement must depend upon the relation of increased width of the channels and the increased number. A great increase in number with but slight increase in width of each would increase pressure, while a slight increase in number with considerable increase in caliber would have the opposite effect. What the exact conditions and result may be in the uterus and placenta cannot be readily ascertained, though it seems likely that some increase in friction must occur. The increased quantity of blood (plethora) assumed to occur in pregnancy is wholly suppositious. Pathologists and physicians have long since ceased to regard plethora as of the importance once ascribed to this condition, and, indeed, there are very good grounds for believing with Cohnheim and others that plethora does not exist otherwise than as a very temporary condition after ingestion of fluids. The

plethora of beer drinkers to which Oertel and Bollinger called attention is probably a frequently repeated and not a stationary condition, and that supposed to exist in "full-blooded" individuals and in pregnant women is very doubtful. If, however, plethora does exist, this fact would give little ground for assuming that the heart's work is increased. Mere increase in the amount of the blood would not directly increase the work of the heart. Whether or not the tissues of the body contain more fluid is aside from the present question; as far as the circulatory blood is concerned, there is much reason to believe that this is but little altered from the normal. If the amount of blood were sufficient to keep the vascular channels in a state of considerable tension, then the work of the heart would be increased, because the expulsive force required of the ventricle rises quickly with the increased distention of the arteries and their corresponding inability to distend farther. Known facts regarding the compensatory mechanisms by which much vascular overloading is preventable, and the direct clinical observations of the peripheral blood pressure in pregnancy, show that such overdistention could not and does not maintain itself. It might be profitable to inquire into the condition of the blood itself to determine whether there is an increase in viscosity of this fluid, for it is the friction of the concentric layers of blood within the vessel upon each other, rather than friction of the blood on the vessel wall, that determines increased resistance to the flow of blood. The evidence regarding viscosity is rather in the direction of a decrease, and therefore of decreased blood pressure, than the reverse.

The direct effect of a growing uterus on the circulation is probably in the direction of increasing the pressure by offering a mechanic impediment to the circulation through the large abdominal vessels. In part the injurious effects of such pressure are obviated by diastasis of the abdominal muscles and general relaxation of the walls, but the resultant is probably in the direction of increased resistance.

The intrathoracic conditions of pregnancy seem to be of such a character as to increase the work of the right ventricle. These conditions are the upward displacement of the diaphragm, the compression of the lungs and the restricted movements of the thorax.

In a measure the comparatively inadequate expansion of the lungs (through insufficient thoracic expansion) neutralizes the other conditions by allowing a dilatation of the pulmonary arterioles, but it is probable that this factor is of slight significance.

Taking into consideration all of the conditions named, it seems doubtful that the work of the heart is increased during pregnancy. If there is an increase it is probably not great, and the fact that women with poorly compensated valvular disease may pass through pregnancy without any loss of compensation almost establishes the contention that whatever increase of work is imposed on the heart falls well within the reserve power of that organ, for even in well-compensated valvular disease there is but little reserve power. When this reserve power is exhausted symptoms of cardiac weakness present themselves; the absence of such symptoms is significant that any additional labor imposed on the heart must be comparatively slight.

There have been a few direct observations of the blood pressure during pregnancy, which would indicate that there is no great variation from the normal. This, of course, is not an absolute measure of the work of the heart, and can, therefore, have only a limited value in determining the question in hand. In addition, it is to be observed that most of the estimations of the blood pressure have been made by means of instruments none too accurate in their results.

3. The Weight of the Heart. Observations of the weight of the heart are usually unreliable, because of the lack of system in removing the great vessels, the pericardium and other appendages. In consequence the figures given by different authors vary widely and no certain conclusions can be drawn regarding pathologic conditions, except in cases in which the increase of weight is very considerable. Kerkring, in 1670, stated that the average weight of the heart in women is 210 grams. Cruveilhier (1724) found the weight to vary from 180 to 210 grams. Tabor (1793) estimated the average weight at 283 grams. Bouillaud, in 14 cases, determined an average of 262 grams and a variation from 200 grams to 350 grams. Lobstein (1835) assumes 255 grams as the medium weight and Gluge (1846) found the average in 4 cases 288 grams, the maximum being 320 and the minimum 250. Wulff

(1856) weighed the hearts of 3 women and found the average 288.4 grams. Clendenning (1838) determined the weight of the heart in 44 women between the ages of twenty and sixty years and found the average 240 grams, the proportion to the total weight of the body being 1 : 187. Reid (1843) found an average weight in 53 cases of 256 grams and a proportion to total body weight of 1 : 176. Peacock (1854) found the average weight for women between twenty and fifty years to be 250.1 grams. Blot (1869) regards as the normal weight 220 to 230 grams. Recently Arnold (1899) weighed the heart in 82 women and found an average of 260 grams, the limits being 225 to 300 grams; and Hamilton found the weight in 4 cases from 283 to 312 grams. Blosfeld (1864), in 8 cases, found an average of 310 grams. Gocke (1883) found an average of 340 grams.

The average of the figures given by the fifteen authors quoted is 263 grams. These figures, however, are certainly high when a comparison is made with the weights obtained by a more accurate method like that of Müller.

H. Vierordt (1890), in a review of the weights of the organs in 2707 cases, found the weights of the heart in women as follows: at twenty-one years (22 cases), 250.6 grams; twenty-two years (19 cases), 251.6 grams; twenty-three years (22 cases), 258.5 grams; twenty-four years (22 cases), 284.1 grams; twenty-five years (26 cases), 260.7 grams.

Müller found average weights in women : twenty to thirty years, 220.6 grams ; thirty to forty years, 234.7 grams ; forty to fifty years, 264.1 grams; fifty to sixty years, 256.9 grams.[1]

A comparison of the weights obtained in normal women with those of the pregnant or parturient shows no certain increase of weight in the latter. Indeed, the evidence is in favor of the con-

[1] The following is a description by Hirsch of the method of Müller for weighing the separate parts of the heart:

The large vessels are first separated close to the valves and the total weight is determined. Then the adipose tissues are carefully separated with forceps and curved scissors. With a certain amount of care this may be done with a residue of not over 8 per cent. (Müller). The ventricles are separated from the septum on a level with the septum, the auricles having been separated exactly in the auriculoventricular groove. The several parts are then weighed separately, and from the comparison of the relation of the total weight of the heart and the total weight of the body the proportional weight is obtained.

It was possible to determine by this method whether the whole organ or any one of its parts was enlarged or decreased in size.

clusion that the weight of the heart is diminished when compared with the total body weight.

Blot (1869) found an average weight of 291.9 grams in 20 puerperal cases; while Loehlein (1876) estimated the average in 9 cases, in which death was due to rupture of the uterus, at 247.2 grams (minimum 202, maximum 312), and in 6 parturient nephritic women at 300.8 grams (minimum 250, maximum 348). When the average of the two series is compared it will be found to correspond closely with that given by Ducrest, one of the early advocates of the hypertrophy theory; and Loehlein's conclusion that the high average obtained by Ducrest was due to inclusion of nephritic cases is justified. MacDonald (1878) weighed the heart in 2 cases of eclampsia and found the figures 269.2 and 255.1 grams.

Letulle found the increased weight of the heart of pregnancy 3 grams at the most.

The most important contribution toward the determination of the comparative weight of the heart in the pregnant and non-pregnant woman is that of Müller. His figures are based upon a study of a series of cases at different periods after labor, some being complicated while others were uncomplicated. The average weight in the non-complicated cases was 227.7 grams. According to the figures cited from various authors this would indicate a distinct reduction in the size, and, according to Müller's own figures, obtained by the more accurate method which he employed, the weight given does not indicate any particular variation from the normal. In all of his cases there was a tendency for the heart index (relation of heart to the total body weight) to fall below the normal, a fact which may, perhaps, be explained upon the ground that the increase in weight at this time is mostly due to deposit of fat. He concludes that the heart, at most, enlarges in proportion to the increase in body weight, but his observations give no support to the claim of Larcher, that there is a distinct hypertrophy during pregnancy. Müller estimated the different portions of the heart separately and found that the relation between the weight of the auricles and the ventricles is slightly altered in favor of an increase in weight of the ventricles, especially the left; but all of the alterations in weight discovered by him were practically within physiologic variations. Hirsch, in reviewing the subject, alludes to the previous observa-

tions of Müller, and adds a case of his own, making in all 22 cases, of which 2 died from ruptured uterus, 1 from placenta prævia and 18 from sepsis. While the average weight was as stated before, not increased and even proportionately diminished, there was one case in which the heart was somewhat increased in size. As all of the patients were ill for some time before death, some proportionate increase by wasting of the muscles of the body might have been expected, but the results showed a reduced heart index.

As far, then, as may be judged by estimations of the weight of the heart, the evidence disproves the assumed hypertrophy, and if the comparative weight or heart index is determined, there seems to be a reduction rather than an increase.

Dreysel, however, claimed that the increase in weight of the heart during pregnancy was 0.44 gram per kilo of increased body weight, which indicates an increase at the rate of 1 : 230, or a slight excess, though not beyond physiologic limits. The result, it will be seen, is somewhat at variance with that given by Müller.

4. The Thickness of the Heart Muscle. Another method of determining whether or not hypertrophy occurs in pregnancy is the estimation of the comparative thickness of the ventricular walls. Larcher claimed to have found an increase of one-quarter to one-third in thickness of the left ventricle, the auricle and the right ventricle remaining normal; and it was upon this conclusion that he based the claim that the heart is hypertrophied during pregnancy. His figures were obtained from a study of 130 pregnant and puerperal women and these results were compared with the normal figures of Laennec. Ducrest also published observations of the same sort. In 97 puerperal cases he found the thickness of the left ventricle to average 15 mm. (maximum 22 mm., minimum 11 mm.). Assuming that Bizot's figures (10 mm.) correctly stated the thickness of the left ventricle in the female, he concluded that the statement of Larcher was confirmed by his own observations. Buhl, however, found the average normal thickness of the left ventricle to be from 16 mm. to 17 mm. and of the right ventricle 6 mm. Gerhardt measured the heart in 2 cases, from which, as well as from his own clinical investigation, he came to the conclusion that there was no hypertrophy or any change in the relationship of the right

and left ventricles. MacDonald found the left ventricle 19 mm. thick in 2 cases of eclampsia. It must be taken into account, however, that these were complicated cases. Engel found the right ventricle disproportionately large in 4 of 5 cases, while, on the other hand, Ducastel found the ventricles normal in 3 of 5 cases.

As far as the determinations of the thickness of the ventricles and other parts of the heart are concerned, it must be confessed that this method seems even less trustworthy than that of determining the total weight of the heart or the weight of different parts. Whatever importance attaches to the method, however, is in disproof of hypertrophy.

A third method, based upon anatomic and postmortem investigation, is that of studying the histologic features with reference to the occurrence of fatty degeneration in the muscle, as it was assumed that if hypertrophy occurred the restitution to the normal after the conclusion of parturition would be by a fatty degeneration. This is a method that was employed by Fritsch. Handfield-Jones also alludes to the fatty degeneration of cardiac involution, but gives no data that may be utilized to determine the occurrence or non-occurrence of hypertrophy during pregnancy.

Physical Examination. If a large number of post-mortem examinations could be made in uncomplicated cases and accurate weights and measurements obtained, the question of the probable occurrence of hypertrophy during pregnancy could be settled. Unfortunately, the cases that come to autopsy are usually complicated in such ways that the data are untrustworthy, and, in addition, the methods generally employed in the past have been liable to considerable error, especially in the direction of overestimating the weight and size.

Under these circumstances the results of physical examination, appealed to by some authorities following Gerhardt's example, are the best evidence that can be obtained, though it must be confessed that percussion is somewhat unreliable, on account of the fulness of the mammary gland, the abdominal distention, and the upward displacement of the diaphragm. Our own studies were arranged so as to exclude, as far as possible, the errors that these conditions might introduce, and, in particular, we invariably repeated the

physical examination after labor so as to eliminate, as far as possible, the effects of mere displacement, while, at the same time, estimating the blood pressure at different times. Before entering upon our own results it may be well to review the literature of this aspect of the problem.

PERCUSSION. The principal support of Larcher's view that has been derived from physical examination is that of Duroziez, whose observations were confined to percussion. He regards the greatest vertical and horizontal diameters of the cardiac dulness as 9 cm. and 12 cm., respectively. His studies, made in 135 cases of pregnancy, gave an excess in the vertical diameter in 95 out of 175 separate determinations made at different periods in the latter part of pregnancy, while the horizontal diameter was excessive in 85 out of 95 examinations. The average measurements were 10 cm. for the ventricle and 15 cm. for the transverse diameter. After parturition he found a rapid subsidence of the hypertrophy in women who did not nurse their children, while a persistent enlargement was sometimes observed in nursing-mothers. In multiparæ permanent hypertrophy was found. Duroziez admits the difficulty experienced in the percussion of the heart in pregnant women, but, notwithstanding this fact, does not hesitate (as Loehlein points out) to state with confidence that there is a return to the normal in the area of dulness on the first day after labor, a recurrence of enlargement on the second day, and greater enlargement on the third day in nursing-women.

Lwoff and Fellner also claim to have detected enlargement on percussion with a gradual return to the normal during the puerperium. Lwoff found the vertical diameter especially increased. The results of Gerhardt are in direct opposition to those of Duroziez, Lwoff and Fellner. While admitting that the lower part of the precordial area is broader than normal, he concluded that the cause of this increase is not any enlargement of the heart, but the upward and anterior displacement of the organ by the increased arching of the cupola of the diaphragm. As a result of this the heart is crowded against the anterior wall of the thorax, the edge of the left lung is displaced and the heart is seemingly hypertrophied. The rapid subsidence of the apparent enlargement after labor and the absence of any indications of increased work of the heart

in the sphygmograms confirmed him in his opinion, while the figures of Larcher and Ducrest seemed to him within physiologic limits.

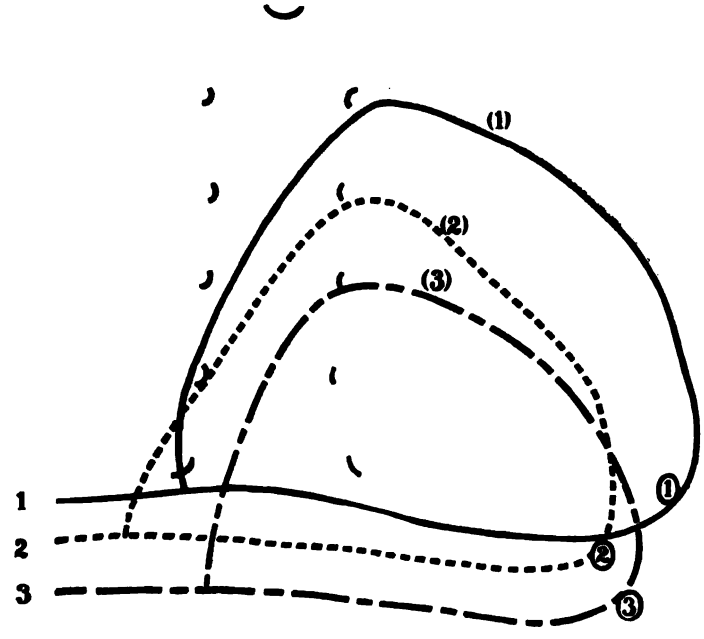
AUSCULTATION. Frequent references have been made by systematic writers to the occurrence of a systolic murmur or *bruit de souffle* over the heart during pregnancy. Larcher himself refers to this in his paper, published in 1859, and alludes to the thesis of Jacquemier (1837), in which particular attention is given to this point. Moreau is quoted by Jacquemier as having observed the same fact. Fritch quite frequently noted a complete replacement of the first heart sound by a murmur in puerperal women, and believed this due to the reduced quantity of blood in the heart. He could make the murmur disappear by causing the patient to sit up and by compressing the aorta or iliac vessels.

Loehlein examined the heart in 375 puerperal cases, finding a murmur in 99, of which 44 had had normal labors and 55 labors attended with considerable hemorrhage. His observations led to the conclusion that heart murmurs are more common after than before childbirth, are best heard from the third to the fifth days, and frequently disappear when the patient rises. They are usually heard at the base of the heart, are systolic and blowing in character and rarely replace the first heart sound completely. In a subsequent series of 156 cases, the cardiac conditions in 98 healthy puerperal women were noted. No murmur was heard in 31 (though some alteration of the first sound was recorded in 11 of these), a feeble and inconstant murmur was heard in 36 cases, and a distinct murmur was found in 31 cases (six times during or immediately after labor, ten times during labor and more distinctly after labor, fifteen times after labor only); altogether, a murmur was audible in 68.3 per cent. of the cases.

Handfield-Jones found a heart murmur in only 5 or 6 of 50 non-anemic multiparæ at the seventh or eighth months of pregnancy.

Marx found a murmur in 27 of 60 healthy pregnant or parturient women. Among the 27 the murmur was found both before and after labor in 14, while it was found in 13 only subsequent to childbirth from the second to the sixth days; 9 of the 14 cases constituting the first group were distinctly chlorotic. The murmur was best heard in the pulmonary area.

Fellner frequently heard an accidental murmur at the apex or less commonly at the base of the heart. He believes this murmur is due to relative insufficiency of the mitral valve. He also refers to the occurrence of a systolic basal bruit. In 95 per cent. of his cases he claims to have detected a distinct and rather rough diastolic murmur to the left of and often under the sternum. This was heard during the last period of pregnancy, but more distinctly in



Outline of heart dulness before labor (1), immediately after labor (2) and two weeks later (3). The position of the suprasternal notch, intercostal spaces at the sternal end and the xiphoid junction are indicated as landmarks.

the early days of the puerperium, sometimes even as late as the tenth day. When heard during labor it seemed to grow louder during the pains, suggesting that increased pressure aggravated the conditions causing the murmur. He does not attempt to decide whether the murmur is a venous one or the result of relative valvular insufficiency.

The character of the first heart sound has been referred to by some writers, and is, of course, a matter of importance. Fellner

found it strikingly soft during the early days of pregnancy, but states that he never observed complete disappearance of this sound among 900 cases. Fritch, on the other hand, refers to cases in which a systolic murmur completely replaced the first heart sound.

The character of the second heart sound is also referred to, though less attention has been given to it than to the first sound. Fellner speaks of the occasional occurrence of a reduplication of the second sound.

PULSE RATE IN THE PUERPERIUM. Slowing of the pulse has been frequently alluded to by obstetricians. Loehlein investigated the question with particular care and found a reduction to 50 in 31 (6.5 per cent.) of 477 cases. Of these, 10 were primiparæ, 18 II-para and 3 III-para. The significance of a slow pulse, and particularly its bearing on the condition of the heart, cannot be stated dogmatically. Undoubtedly a number of influences play a part in the alteration of the rate. Among other influences, exhaustion in particular seems to be important.

Our own studies of the heart and circulation in and after pregnancy were entirely clinical, and embraced physical examinations before and after labor, with determinations of blood pressure and sphygmograms.

We have before alluded to the difficulties encountered in percussion of the outlines of the heart on account of the fulness of the mammary gland. With care, however, fairly satisfactory results could be obtained, and at all events the comparative outlines before and after labor showed the altered conditions represented in the accompanying illustration, and are also shown in the tables giving details regarding the physical examination. The outlines of the heart were obtained by first carefully marking its borders with oil, using a fine camel's-hair brush, and then pressing tissue paper against the skin so as to transfer the markings to the paper. Copies of these outlines were then made on heavier paper. A typical outline is selected for reproduction.

Our cases are separated into three groups: (1) primiparæ, of which there were 39; (2) multiparæ, of which there were 21; and (3) complicated cases, of which there were 10. We have excluded

these complicated cases from the tabulations because there was either cardiac or renal disease antedating pregnancy. These cases, however, are instructive in showing that the effect of pregnancy upon the heart is comparatively slight, since the conditions present were such that any considerable strain must have produced a decided effect on the heart, which, however, was not observed.

SYNOPSIS OF PRIMIPARÆ.

Number of cases	39
Ages	from 16 to 35 years.
Upper border before labor, at second rib	in 35 cases.
Upper border before labor, at third rib	in 4 cases.
Upper border after labor, at third rib	in 22 cases.

(In all of these cases it had been at the second rib.)
Upper border after labor, unchanged, in 17 cases.

Apex before Labor.

In third interspace	8
In fourth interspace	28
In fifth interspace	3

Apex after Labor.

In fourth interspace (moved down)	5
In fifth interspace "	22
Unchanged	12

Murmurs.

Only before labor	7
Only after labor	7
Doubtful before and negative after labor	1
Doubtful before and positive after labor	1
Positive before and doubtful after labor	1
Murmur both before and after labor.	15
No murmurs at any time	7

The murmurs were purely systolic in time, with one exception. In this the murmur was heard midway between the first and second sound.

TABLE I.

No.	Before labor.			After labor.			Before.	After.	Before.	After.	Remarks.
	Right border.	Upper border.	Left border.	Right border.	Upper border.	Left border.	Apex	Apex	Murmur	Murmur	
1	—R. sternum	2d rib	—M.-cl.	No change	3d rib	No change	3d	4th	Yes	No	Age 19. Pulsation seen and felt in 1st and 2d interspaces before labor; in 2d, after labor murmur heard at base; recti separated.
2	+R. "	2d "	M.-cl.	R. sternum	3d "	No change	4th	4th & 5th	"	Yes	Age 18. In labor when first seen; murmur not heard 10 days after labor; recti not separated.
3	Mid. "	2d "	—M.-cl.	No change	3d "	No change	4th	5th	"	"	Age 20. Murmur not present on tenth day; always basal; recti slightly separated.
4	+R. "	2d "	+M.-cl.	—R. sternum	3d "	M.-cl.	3d	4th	"	"	Age 25. Pulsation seen in 2d interspace; murmur basal; 2d pulmonic rather loud before delivery; split after.
5	L. "	3d "	—M.-cl.	Mid. "	No change	No change	4th	5th	No	"	Age 17. Examination before delivery uncertain; patient in pain; forceps delivery; recti separated.
6	R. "	2d "	M.-cl.	Mid. "	3d rib	—M.-cl.	4th	4th	Yes	"	Age 22. Pulsation in 2d interspace before and after labor; recti separated; murmur basal.
7	—R. "	3d "	—M.-cl.	No change	No change	No change	4th	5th	"	"	Age 21. Murmur at base only before labor; over body of heart after labor.
8	+R. "	1st interspace	+M.-cl.	—R. sternum	3d rib	—M.-cl.	3d	5th	No	"	Age 25. Apex in third interspace anterior axillary line, moved down after rupture of membranes and still more after delivery; murmur eight days after delivery.
9	+R. "	2d rib	M.-cl.	Mid. "	3d "	No change	4th	5th	"	"	Age 22. Murmur heard second day after labor; second pulmonic reduplicate after delivery.
10	+R. "	2d "	M.-cl.	No change	No change	No change	4th	4th	"	No	Age 19. Second examination eight hours after labor; no subsequent examinations on account of sore breasts; recti separated.
11	L. "	2d "	+M.-cl.	Mid. sternum	3d rib	M.-cl.	4th	5th	Yes	Yes	Age 20. Entire heart was apparently pushed upward and to the left.
12	L. "	2d "	+M.-cl.	No change	No change	No change	5th	5th	No	No	Age 19. Case of twins; abdomen very large; only one examination made after delivery; thirteen hours.
13	R. "	2d "	—M.-cl.	Mid. sternum	No change	No change	3d	4th	"	Yes	Age 20. Murmur noted on tenth day; shape of ribs peculiar, curve great, 2d rib low in position; recti separated.
14	Mid. "	2d "	M.-cl.	No change	2d rib	No change	4th	3d	Yes	"	Age 26. Has had two miscarriages; pulsation visible in second interspace after labor; recti not separated.
15	R. "	2d "	+M.-cl.	" "	No change	No change	4th	5th	"	"	Age 27. Has had one abortion; only examined once after delivery.
16	+R. "	2d "	M.-cl.	R. sternum	3d rib	No change	4th	5th	?	"	Age 19. Repeated observations were made of this patient; she did not nurse child; murmur absent two weeks after delivery.
17	R. "	2d "	—M.-cl.	No change	No change	No change	4th	4th	Yes	No	Age 20. The note under left clavicle is impaired and breathing is harsh; for three weeks after delivery she had an irregular fever for which no cause could be found.

18	+R. sternum	2d rib	+M.-cl.	R. sternum	No change	No change	3d	4th	Yes	?	Age 28. Has had several abortions; first child carried to term; heart dulness large; only two examinations made.
19	R. "	2d "	M.-cl.	R. "	3d rib	—M.-cl.	4th	5th	"	Yes	Age 19. Forceps delivery.
20	R. "	2d "	M.-cl.	—R. "	3d "	—M.-cl.	3d and 4th	5th	"	No	Age 18. The change in outline not noted until some days after delivery; delivery by forceps.
21	R. "	2d "	M.-cl.	No change	3d "	—M.-cl.	4th	4th	No	"	Age 20. This girl developed typhoid fever almost immediately after delivery.
22	R. "	2d "	M.-cl.	Mid. sternum	3d "	M.-cl.	4th	5th	"	Yes	Age 19. Very little change noted in outline until the tenth day; murmur appeared on third day.
23	R. "	2d "	M.-cl.	No change	2d interspace	—M.-cl.	3d	5th	Yes	"	Age 21. The diminution in dulness was most marked above and to the left.
24	R. "	2d "	+M.-cl.	" "	No ch'ge	No ch'ge	3d and 4th		No	"	Age 25. Second pulmonic split after labor.
25	R. "	2d "	+M.-cl.	" "	No change	No change	4th and 5th		Yes	"	Age 23. Murmur always basal; only two examinations.
26	R. "	2d "	M.-cl.	Mid. sternum	3d rib	—M.-cl.	3d	4th	"	"	Age 18. Second pulmonic reduplicated after labor; murmur only apical before labor, afterward heard over entire heart.
27	R. "	2d "	—M.-cl.	Mid. "	3d "	No change	4th	5th	"	No	Age 29. Murmur disappeared after "dropping," the effect of which was to lessen area of dulness.
28	—R. "	2d "	+M.-cl.	Mid. "	3d "	M.-cl.	4th	5th	"	Yes	Age 29. Pulse rate very slow; murmur transmitted to axilla before and just after labor; later disappeared.
29	L. "	3d "	M.-cl.	No change	No ch'ge	No ch'ge	4th	5th	"	"	Age 35. Heart area unusually small.
30	R. "	2d "	M.-cl.	" "	No change	No change	4th & 5th	4th & 5th	No	"	Age 23. Only two examinations made, the second 8½ hours after delivery; no change noted except murmur.
31	R. "	3d "	M.-cl.	" "	No change	No change	4th	5th	"	No	Age 18. Second examination made seven days after delivery; the apex was found lower down; no other change.
32	R. "	2d "	+M.-cl.	" "	No change	No change	4th	5th	Yes	Yes	Age 22. Great distention at second examination eight hours after delivery; subsequent examination impossible; inflamed breast.
33	+R. "	2d "	M.-cl.	R sternum	3d rib	No ch'ge	4th	5th	?	No	Age 26.
34	—R. "	2d "	M.-cl.	No change	No change	No change	4th	4th	Yes	"	Age 16. Pulsation visible in second interspace before labor, not after; at second examination, ten hours after delivery, abdomen was very tympanitic.
35	+R. "	2d "	M.-cl.	—R. sternum	2d interspace	No change	3d & 4th	4th	No	"	Age 20. Pulsation visible and palpable in second and third interspaces; second examination four hours after labor.
36	R. "	2d "	+M.-cl.	No change	No change	No change	4th & 5th	5th	"	"	Age 25. Dulness appears large on account of peculiar bulging of chest; second examination twenty-four hours after forceps delivery.
37	R. "	2d "	M.-cl.	—R. sternum	3d rib	—M.-cl.	4th	5th	Yes	"	Age. 24.
38	+R. "	2d "	M.-cl.	Mid. sternum	3d "	No change	5th	5th	No	"	Age 26. Forceps delivery; several examinations show well the diminution of dulness to the right and above after labor.
39	R. "	2d "	M.-cl.	" "	3d "	—M.-cl.	4th	5th	Yes	"	Age 16. Shows well change of dulness above and to the left after labor; recti slightly separated.

TABLE II.

No.	Before labor.			After labor.			Before.	After.	Before.	After.	Remarks.
	Right border.	Upper border.	Left border.	Right border.	Upper border.	Left border.	Apex	Apex	Murmur	Murmur	
1	R. sternum	3d rib	—M.-cl.	Mid. sternum	No change	No change	3d	3d & 4th	No	No	Age 18. Para II. Pulsation felt in 2d interspace after labor; recti separated after labor; not demonstrable before.
2	R. "	2d interspace	M.-cl.	Mid. "	No change	No change	4th	5th	"	Yes	Age 30. Para V. Murmur heard only at 2d left interspace; recti not separated.
3	+Mid. "	3d rib	—M.-cl.	No change	No change	No change	4th	5th	Yes	No	Para II. In pain for 36 hours when first examined; labor very long; uterine inertia; recti split.
4	R. "	2d "	M.-cl.	Mid. sternum	3d rib	No change	3d & 4th	4th & 5th	No	Yes	Age 32. Para III. The murmur is peculiar in that it is just between 1st and 2d sounds at apex; no murmur at base; 2d pulmonic split.
5	R. "	2d interspace	M.-cl.	Mid. "	3d interspace	No change	5th	5th	Yes	"	Age 29. Para III.
6	R. "	3d rib	M.-cl.	No change	No change	No change	3d & 4th	3d & 4th	"	"	Age 27. Para III. Second examination four hours after delivery; beat less forcible and murmur less loud after delivery.
7	R. "	2d "	M.-cl.	" "	No change	No change	5th	5th	"	"	Age 21. Para II. Second examination 2½ hours after delivery; murmur basal.
8	R. "	2d "	M.-cl.	" "	No change	No change	4th	4th	"	"	Age 30. Para IV. Second examination two hours after delivery; pulsation in 2d left interspace before and after labor.
9	—R. "	2d "	M.-cl.	Mid. sternum	2d rib	No change	4th	5th	"	"	Age 24. Para IV. Murmur present after being out of bed; pulsation in 2d interspace to left before labor.
10	+R. "	2d "	M.-cl.	R. sternum	3d rib	No change	4th	5th	"	"	Age 25. Para II. 2d pulmonic split after labor.
11	Mid. "	2d interspace	M.-cl.	No change	No change	No change	4th	5th	?	No	Age 22. Para II. In labor and membrane ruptured when first seen; recti split after labor.
12	R. "	2d interspace	—M.-cl.	" "	3d rib	—M.-cl.	4th	5th	Yes	Yes	Age 20. Para II. Before labor area small, great tympany, no liver dulness; after labor heart area much larger below.
13	+Mid. "	3d rib	M.-cl.	Mid. sternum	No change	—M.-cl.	4th & 5th	4th & 5th	"	"	Age 33. Para II. Forceps delivery; much hemorrhage; recti not split.
14	Mid. "	3d "	M.-cl.	No change	No change	No change	4th	4th	"	No	Age 26. Para III. Membranes ruptured and patient in pain when examined first; recti separated.
15	Mid. "	2d "	M.-cl.	" "	No change	No change	4th & 5th	4th & 5th	"	"	Age 20. Para II. The area of dulness is very large; no other evidences of organic disease.
16	+Mid. "	2d "	M.-cl.	" "	3d rib	No change	4th	5th	"	Yes	Age 25. Para II.
17	+R. "	2d "	—M.-cl.	Mid. sternum	3d "	No change	4th	5th	No	"	Age 20. Para II. After labor there was a pulsation in 2d left interspace where murmur was heard; recti split.
18	Mid. "	2d "	M.-cl.	No change	No change	No change	4th	5th	Yes	"	Age 37. Para VI. Second examination 23 hours after delivery.
19	+R. "	2d "	M.-cl.	R. sternum	No change	No change	4th	5th	No	No	Age 30. Para II. Patient of Dr. Norris, Preston Retreat.
20	R. "	3d "	—M.-cl.	No change	No change	No change	4th	4th	Yes	Yes	Age 22. Para II.
21	L. "	2d "	+M.-cl.	Mid. sternum	3d rib	—M.-cl.	3d	4th	"	"	Age 22. Para II. Pulsation in 2d left interspace before and after labor.

SYNOPSIS OF MULTIPARÆ.

Before.

Number of cases	21
Upper border at second rib	in 12
Upper border at third rib	in 9

After.

Upper unchanged	in 14
Upper moved down	in 7

Apex Beat before Labor.

In third interspace	in 2
In fourth interspace	in 16
In fifth interspace	in 3

Apex Beat after Labor.

Moved down	in 13
Unchanged	in 8

Murmurs.

Only before labor	3
Only after labor	3
Doubtful before and none after	1
Murmur both before and after	12
No murmurs at any time	2

In many of these cases a pulsation was noted to the left of the sternum in the second and third interspaces and a split second sound was audible in the same area. The murmur was usually heard best at the base, though it was often audible over the entire cardiac area.

The most notable change in the cardiac dulness after labor was a diminution in the breadth of the upper portion, causing the extension to the left in the second and third interspace to decrease decidedly. This would correspond with a subsidence of distention of the conus arteriosus and root of the pulmonary artery.

In practically every case the costal angle was greatly increased before delivery and the liver dulness was diminished, so that in many instances only a slight change of note indicated the passage from pulmonary resonance to abdominal tympany.

SUMMARIES OF BLOOD-PRESSURE ESTIMATIONS.

1. *Primiparæ.*

Before labor (average of 18 cases; Riva-Rocci, narrow cuff)	$123\frac{5}{18}$ mm.
After labor (average of 18 cases; Riva-Rocci, narrow cuff)	$122\frac{3}{18}$ mm.
Before labor, highest pressure observed	140 mm.
Before labor, lowest pressure observed	96 mm.
After labor, highest pressure observed	140 mm.
After labor, lowest pressure observed	103 mm.

The lowest pressure, 96 mm., occurred in Case 36, in which the pressure was 130 twenty-four hours after delivery, falling to 103 two days later, subsequently rising to 113, when the patient left her bed. Ergot was administered during labor.

ESTIMATIONS OF PRESSURE DURING AND AFTER LABOR.

			Pulse.
Case 2.	Before labor, between pains	121 to 131 mm.	68 to 96
	Immediately after labor	141 mm.	56

The estimations were as follows:

	Before Labor.	
July 6, 1903, 11 A.M.	121 to 131 mm.	68 to 96
	After Labor.	
July 6, 1903, 4.30 P.M.	141 mm.	56
" 7, " 10.30 A.M.	122 mm.	
" 8, " —— P.M.	128 mm.	
" 9, "	120 mm.	
" 17, "	130 mm.	
" 27, "	140 mm.	

Case 5.	During labor	120 to 140 mm.	84 to 90
	Forty-eight hours later	127 mm.	72
	Two weeks later	140 mm.	84

SUMMARIES OF BLOOD-PRESSURE ESTIMATIONS.

		Pressure.	Pulse.
Case 8.	During labor (membranes ruptured)	105 to 122	88
	Twenty-four hours after	103½	92

Breech wedged in; labor, 48 hours; ether; much blood lost.

Case 13.	Week before labor	130	
	In labor four hours	175 to 185	56
	Four and one-half hours after forceps operation	160 to 165	52
	Twenty-four hours later	135	60
	Ten days later; out of bed	142	100

This patient had no binder or ergot, but was given f ℥ iss sherry during labor.

		Pressure.	Pulse.
Case 20.	Three weeks before labor . . .	139	80
	In labor twelve hours, pains slight . .	118	96 to 102
	Ten hours after forceps . . .	130	
Case 19.	Four days before labor	112	
	In labor	110 to 126	
	Three hours after forceps . . .	112	
Case 29.	Week before labor	119⅘	100
	In labor, between pains	142	80
	After labor twenty-one hours . . .	118	60
	After labor, ten days	125	64
	After labor, thirteen days . . .	132	72

This patient was in bed a long time. She had a repair of perineum and an abscess in the thigh as a result of ergot injection.

2. *Multiparæ.*

Fifteen cases before labor by Riva-Rocci; narrow cuff averaged .	$122\frac{4}{15}$
Fifteen cases after labor by Riva-Rocci; narrow cuff averaged .	$121\frac{9}{15}$
Highest pressure before (same case)	163
Highest pressure after (same case)	140
Lowest pressure before	91
Lowest pressure after	100

Blood Pressure in Pregnancy. Unfortunately these observations were made before it was known that the width of the rubber cuff used in compressing the arm influences the determination. It is proper also to state that as the figures here given are only those representing systolic pressure, the absolute condition of blood pressure is not accurately indicated. At the time that these studies were made we lacked satisfactory apparatus for determining diastolic pressure. The figures given below to show the comparative determinations of Riva-Rocci, Gärtner and Hill and Barnard roughly indicate the diastolic pressure in the Hill and Barnard figures, but the narrow cuff and other imperfections made these figures too high. Measurements were made with the apparatus of Riva-Rocci (with the usual one and one-quarter inch cuff), the Gärtner tonometer, the Oliver instrument, and in some instances the greatest pulsation was noted according to the plan of Hill and Barnard. In practically all instances (except where the Oliver instrument was used) the measurements were made with the Gärtner mercury manometer.

The normal blood pressure in adult women has been estimated by a number of observers. Gumprecht (*Zeit. f. klin. Med.*, Bd.

xxxix., Heft 5 and 6) found the average with the Riva-Rocci apparatus to be 120 mm. Hensen (*Deutsches Archiv f. klin. Med.*, Bd. lxvii., Heft 5 und 6) using the same apparatus found the average pressure in 30 healthy working-women to be 132 mm. Doleschal (*Inaug. Dissert.*, 1900) using Gärtner's tonometer found the average pressure in 100 persons to be 120 mm.; while Weiss (*Münch. med. Woch.*, 1900, Nos. 3 and 4) found the average pressure in women to be 100 mm. with the tonometer.

Taking Gumprecht's and Hensen's figures as a basis, the results obtained in our cases would show the average to be within normal limits, though great variations occurred in the individual. Thus, in 18 primiparæ the Riva-Rocci instrument showed an average pressure of $123\frac{5}{18}$ in the week preceding delivery, while in 17 multiparæ the average was $122\frac{8}{17}$.

In primiparæ the variations were between 96 mm. as the lowest and 140 mm. as the highest. In multiparæ the lowest reading was 91 mm. and the highest 163 mm.

These pressures were all taken under the same conditions as to position, etc., and on women who were apparently healthy. The patients, however, varied in weight from 100 to 150 pounds and presented all degrees of physical vigor from the very robust to the very delicate. The influence of physique on blood pressure is uncertain, but it seems evident that a delicate girl of eighteen would not show the same degree of blood pressure as a vigorous woman of thirty who had worked hard until the time of admission.

There seemed to be very little reason, either from physical examination, blood-pressure estimations or from the numerous pulse tracings which were made to believe that pregnancy, *per se*, is a cause of heightened pressure.

In two instances, where the pressure was at the upper bounds of the normal, the abdominal muscles were found to be unusually tight after delivery, suggesting the possibility of an influence on the pressure due to a heightened intra-abdominal tension. This is borne out by the fact that the upper border of heart dulness was higher in primiparæ. The rule was to find a more or less well-marked separation of the recti muscles which persisted for a considerable time after delivery. Also, as the high pressures were found in women with good-sized arms it is probable that the

disproportion between the size of the arm and the width of the cuff had a certain effect.

Concerning the use of the Gärtner instrument, it may be stated that it was, on the whole, unsatisfactory. In almost all cases its results were higher than those obtained by the Riva-Rocci apparatus, and for this difference no satisfactory explanation could be found.

It may be of interest to show the comparison of estimations obtained with different instruments.

COMPARISON OF THE GÄRTNER AND RIVA-ROCCI INSTRUMENTS.

CASE 8. May 2, 1903.

Gärtner,		Riva-Rocci,	
"	105	"	110
"	104	"	108

May 16, 1903. In labor; membranes ruptured four hours. Pulse, 88.

Gärtner,		Riva-Rocci,	
"	116	"	122
"	130	"	120
"	117	"	110
"	135	"	105
"	110		
"	130		
"	130		
"	120		

May 19, 1903, 12 noon. Pulse, 92.

Gärtner,		Riva-Rocci,	
"	95	"	105
"	110	"	101
"	98	"	103
"	105		

CASE 9. Flush slow.

Gärtner,		Riva-Rocci,	
"	112	"	100
"	125	"	103
"	117	"	105
"	124	"	100
"	90		

CASE 15. Skin of finger thick; slow flush.

Before Labor.

Gärtner,		Riva-Rocci,	
"	105	"	126
"	105	"	120
"	110	"	122

Skin of finger now soft. Second series of examinations two weeks after first and eight hours after labor. Temperature, 99°.

After Labor.

Gärtner, 145	Riva-Rocci, 135
" 135	" 136
" 142	" 135
" 135	

CASE 16.

Gärtner, 108	Riva-Rocci, 112
" 115	" 115
" 120	" 113
" 135	" 115
" 130	" 112
" 135	
" 123	

CASE 24. Pulse, 56. Perhaps the slow pulse accounts for great difference between pressures.

Gärtner, 126	Riva-Rocci, 110
" 140	" 112
" 150	" 115
" 126	" 112
" 125	
" 140	
" 128	
" 132	
" 140	
" 132	

CASE 26. Absolutely no reason for difference was discovered.

Gärtner, 135	Riva-Rocci, 112
" 136	" 107
" 136	" 111
" 140	" 113
" 137	

Comparisons similar to this might be given in any desired number, but these are purposely selected because in each instance there were present the most favorable conditions for use of the tonometer: thin skin; well-fitting ring; quiet patient accustomed to use of these instruments; recumbent position, and the same manometer with both forms of instrument. In many instances the figures agree almost perfectly. More often we found the variations so great on repeated trials with the Gärtner instrument that as many as ten observations were taken to obtain an average. The first pressures of a series were sometimes high, at other times low, no constant behavior being found. The flush seemed to be affected in a measure by the degree of primary pressure established before

removing the rubber band. When this was excessive the results were lower than when the primary pressure was only slightly greater than that at which flush appeared. On one occasion (not a case of pregnancy) there was difficulty in getting any flush; this was a case of shock and excessive hemorrhage, due to a crush of thigh. There is but little difference in the time required to make the examination with the two instruments.

COMPARISON OF GÄRTNER, RIVA-ROCCI, HILL AND BARNARD AND OLIVER.

Julia C., aged twenty-five years. Pregnant second time. Soft systolic murmur over base, with slight accentuation of pulmonic second sound.

Gärtner.	Riva-Rocci.	Hill and Barnard.	Oliver.
130	130	120	125
128	130	115	(Average from
110	130	110	several observa-
125	125	110	tions.)
123	125		
	Same Patient, Forty-eight Hours after Delivery		
120	122	100	100
115	124	100	(Average.)
125	126	105	
111			
121			
120			

COMPLICATED CASES.

The following summaries are given to show the state of the circulation in cases in which serious weakening of the heart would have occurred were the conditions such as has been asserted to exist during pregnancy. The normal course of events, however, indicates the falsity of that assumption, and supports our belief that there is no special strain upon the heart during pregnancy; and hypertrophy, if it exists, must be due to other causes.

CASE 1. *Nephritis complicated with hydramnios.*—Mrs. Martha K., aged thirty-four years, white; second pregnancy. Examined May 14, 1902. She gives a history of eclampsia in her former labor. Two weeks previous to admission she began to have swelling of the hands and feet and albumin, one-fifth by bulk, in the urine. The patient is small and thin, with peculiarly shaped ribs, so curved that the interspaces seem displaced. The abdomen is

tense, and the irregularity suggests twins. The heart is not enlarged. The apex is in the third interspace (which, owing to the extreme curve of the ribs, is about equal to the fourth interspace at the edge of the sternum) and inside the midclavicular line. No murmurs are heard. The second aortic sound is accentuated. Blood pressure by the Riva-Rocci on April 13th varies between 160 and 165. On April 14th, one hour after a vapor bath, it varies between 138 and 160 (patient is having slight pains).

15*th*. Second examination twelve hours after delivery. Patient has on a firm binder and pad. The condition proved to be hydramnios, with a large placenta. No murmurs are heard. The aortic second sound is still loud. Blood pressure by the Riva-Rocci, between 178 and 180. Pulse, 56. She is having slight after-pains. The heart has moved down slightly.

26*th*. Heart dulness still farther down, the apex being in the fourth interspace (equivalent to the fifth at the margin of the sternum). A short systolic murmur is now heard just inside the apex. This is not transmitted. Second sound is not so loud. Blood pressure by the Riva-Rocci, 125 to 130; pulse, 68. The patient made an uninterrupted recovery. The most notable feature, as far as the circulation is concerned, was the high blood pressure.

CASE 2. *Nephritis, uremia.*—Mrs. H., aged twenty-six years, white; second pregnancy. Examined April 29, 1902. The patient is very edematous, and has the appearance of a nephritic. The previous labor showed only a slight edema. There is no history of cardiac symptoms before pregnancy. Cardiac dulness begins above at the upper border of the second rib and extends to the right border of the sternum and to the midclavicular line on the left, where the apex is found in the fourth interspace. Over the dulness to the left of the sternum, best marked at the apex, there is heard a systolic murmur transmitted toward the axilla. Both second sounds are loud. The urine coagulates almost entirely on boiling. Blood pressure by the Gärtner, 190 to 195; by the Riva-Rocci, 185 to 190.

11*th*. Second examination made eight hours after delivery. There is practically no change in the heart outlines or sounds. Murmur is perhaps more distinctly heard. She is even more edematous, is uremic and has a bronchitis. The blood pressure was taken

frequently, but the presence of the edema and the frequent cough made the results unreliable. Though on treatment by vapor baths, enemata of salt solutions, cathartics, etc., there has been no improvement. This patient, after a long illness, left the hospital in good condition. Very high blood pressure was notable.

CASE 3. *Nephritis (?), albuminuria.*—Mrs. Lizzie R., aged thirty-seven years, white; eighth pregnancy. Examined April 30, 1902. Former labors were uneventful, and the present pregnancy showed no abnormality until five weeks before admission, since which time she has been in bed on account of albuminuria. The patient is thin, but the abdomen is of the usual size and tension. There is some edema and some enlargement of the veins of the leg, which, she says, has been present during earlier pregnancies. Heart dulness begins above at the lower border of the second rib, on the right to the right border of the sternum, on the left to just inside the midclavicular line, where the apex is felt in the fourth and fifth interspaces. Over the apical region there is heard a short systolic murmur, which is not transmitted. The second sounds are not especially loud. Blood pressure by the Riva-Rocci varies between 128 and 130, by the Gärtner between 110 and 125. The pulse is 118.

Second examination made fifteen hours after labor, which was not unusually long or hard and during which nothing abnormal occurred. The heart dulness is somewhat lower. The breadth of the dulness is not changed. The short systolic murmur is as before. Blood pressure: Gärtner, 98 to 110; Riva-Rocci, 118 to 120. Pulse, 108.

May 2d. Area of dulness unchanged. Murmur at apex still present. Just to the right of the apex the first sound seems to be split. Blood pressure: Gärtner, 90 to 105; Riva-Rocci, 110 to 120. Pulse, 108.

4th. Blood pressure: Gärtner, 132 to 141; Riva-Rocci, 130 to 137. Pulse, 96 to 100.

21st. To-day no murmur can be heard. The patient feels very well. Blood pressure: Gärtner, 105 to 112; Riva-Rocci, 102 to 110. The patient's recovery was apparently perfect.

CASE 4. *Mitral regurgitation.*—Allen P., aged eighteen years, colored, primipara. Examined March 25, 1902. She gives a

rather doubtful history of shortness of breath and swelling of the feet, even before pregnancy. The chest is small, but well formed, and the abdominal distention is about normal. Cardiac dulness begins above at the top of the first rib and extends on the right to a full finger's breadth beyond the right sternal border, on the left to the anterior axillary line and below to the fifth rib. On palpation the apex is felt in the fourth interspace, but almost as strong a pulsation is felt in the third interspace, and in the second interspace, close to the sternum, there is a visible systolic pulsation. All these pulsations are more evident on sitting. No murmurs are heard, but the second pulmonic sound is somewhat accentuated.

26*th*. The blood pressure by the Riva-Rocci varies between 115 and 120; by the Gärtner, between 125 and 140.

27*th*. Second examination made six hours after labor. The area of heart dulness has moved down about an interspace, and extends less to the right. The apex is now most strongly felt in the fifth interspace, though pulsations in the upper interspaces are still apparent. Over practically the entire area of dulness a distinct systolic murmur can be heard, with, perhaps, most intensity at the apex. The second pulmonic sound is as before.

April 8th. Third examination shows no change in the outlines. The systolic murmur is now heard only when the patient sits up, and is not transmitted. The second sounds are both loud. In the sitting posture the pulsation in the second interspace is still visible. Blood pressure: Riva-Rocci averages 112; Gärtner averages 130.

CASE 5. *Mitral regurgitation.*—Florence G., aged seventeen years, colored, primipara. Examined September 2, 1902. Girl is of medium size and well nourished. The abdomen is normal in size and tension. No separation of the recti muscles demonstrable. She states that she has never had dyspnea, palpitation or edema. Heart dulness above extends to the lower border of the second rib; on the right to midsternum; on the left to the midclavicular line, where the apex is in the fourth interspace. Distinct pulsation is felt to the outer side of the left line of dulness and over practically the entire area to the left of the sternum, especially in the second interspace. Over the area of dulness, and most marked at

the apex, can be heard a blowing systolic murmur, which is transmitted to and plainly heard in the axilla. The second pulmonic sound is accentuated. Blood pressure by the Riva-Rocci varies between 120 and 125; pulse 80.

5th. Second examination made one hour after delivery, which presented nothing unusual. There is but little change. The apex is now in the fifth interspace and the pulsation in the second left interspace is no longer visible. The murmur is as above described. Blood pressure by the Riva-Rocci varies between 145 and 150. No ergot or binder used in this case.

CASE 6. *Mitral regurgitation.*—Esther B., aged twenty-four years, colored; third pregnancy. Examined April 10, 1902. Patient is short and stout, with a thick chest wall. Says that she is naturally "short-winded," but no more now than is usual. The abdomen is rather larger than normal. Cardiac dulness begins above on the upper border of the first rib, on the right it extends to a finger's breadth beyond the right sternal margin, on the left about one-half inch beyond the midclavicular line. Apex is in the fourth interspace and above in the third can be felt a distinct pulsation. In the second left interspace close to the sternum can be heard a short systolic murmur, which seems very close to the ear. The second pulmonic sound is accentuated. Blood pressure varies between 122 and 135 by the Gärtner; between 122 and 125 by the Riva-Rocci.

17th. Second examination made thirty hours after labor, at the end of which a repair under ether was made. The shortness of breath is no longer present and the patient lies more comfortably. The heart dulness extends less far to the left and the apex beat is lower down in the fifth interspace. The murmur so close to the ear before noted in the second left interspace can no longer be heard, but over the entire area of dulness to the left of the sternum can be heard a systolic murmur, which is, perhaps, best marked at the apex. The second pulmonic sound is accentuated and the closure of the valve can be distinctly felt. Blood pressure: Gärtner averages between 105 and 115; Riva-Rocci between 110 and 113.

27th. Third examination shows the same area of dulness as the second. In the recumbent position there is heard a soft systolic

murmur just inside the apex and the second pulmonic sound is accentuated and split. In the erect position the murmur is indistinct, but the split second is unchanged. Patient still complains of some shortness of breath, but there is no edema or palpitation. Evidently there was an organic lesion with some dilatation before labor, but no sign of failure of compensation during delivery.

CASE 7. *Mitral regurgitation; uterine hemorrhage.*—Martha L., aged twenty-four years, colored; fifth pregnancy. Examined August 4, 1902. Former labors were easy, but she has always had some swelling of the feet and shortness of breath while carrying the child. Patient is tall and well built; abdomen normal in size; says that "dropping" has occurred. During the present pregnancy many varicose veins have developed on the lower extremities and genitals, and she has been short of breath. Heart dulness begins above at the lower border of the second rib, extends on the right to a little beyond the right sternal border, on the left to a finger's breadth beyond the midclavicular line. Apex is seen and felt in this line in the fifth interspace. A systolic pulsation is also noted in the second left interspace close to the sternum and over the left border of the heart. At the apex there is heard a systolic murmur which is transmitted to the axilla, and is also heard over the body of the heart, especially at the pulmonic area, where the second sound is markedly accentuated. Blood pressure: Riva-Rocci, 120 to 123; greatest pulsation at 90.

9th. Second examination made twenty-two hours after labor, which was unusually easy, lasting only four or five hours. There was no evidence of circulatory failure. During the night a rather severe uterine hemorrhage occurred. Area of heart dulness unchanged. Pulsation still seen in the second left interspace. Murmur as before—long, blowing, and transmitted to the axilla. Blood pressure: Riva-Rocci, 125 to 130.

20th. Blood pressure by Riva-Rocci 130. No change in heart.

21st. Blood pressure, Riva-Rocci, 128 to 130; heart as before. This is a typical case of mitral regurgitation, yet the labor was perfectly normal, except for the hemorrhage following it, which, perhaps, may have eased the circulation.

CASE 8. *Mitral regurgitation.*—Sydney S., aged twenty-five years, colored; second pregnancy. Examined February 24, 1902.

The patient is short and fat. The tension of the abdominal wall and the size of the fetus are normal, but the quantity of liquor amnii is plus. She has had dyspnea and swelling of the feet for some time, even before pregnancy.

The area of cardiac dulness is greatly increased, beginning above at the top of the second rib, on the right at right margin of the sternum, on the left almost at the anterior axillary line. Apex is in the fifth interspace. Over the entire precordia, most marked at the apex, there is a systolic murmur which is transmitted to the axilla. The second pulmonic sound is accentuated. Blood pressure varies between 115 and 120 by the Riva-Rocci; greatest pulsation occurs between 90 and 100.

March 17th. Second examination made eight hours after delivery, which was easy, lasting only seven hours. There is but little change in the total area of heart dulness. The second tracing gives the impression that the entire heart had been pushed slightly upward and to the left. The systolic murmur presents the same characteristics as before. Blood pressure 125 to 130 by the Riva-Rocci. This is also a case of mitral regurgitation in which labor apparently produced no bad results.

CASE 9. *Mitral regurgitation.*—Mary B., aged twenty-five years, white; second pregnancy. Examined March 4, 1902. The patient is very small, weighing only 112 pounds, and has had cardiac symptoms for some time. The area of heart dulness is markedly increased, beginning above at the upper border of the second rib, extending to a full finger's breadth beyond the right sternal margin, and on the left to the anterior axillary line. Over the entire area of dulness to the left of the sternum there is visible and palpable pulsation. Apex in third and fourth diffuse. Over same extent can be heard a systolic murmur which is, perhaps, best marked at the third left chondrosternal junction. At this point the murmur has a peculiar whistling quality and is apparently very close to the ear. At other points the murmur is dull. Blood pressure by the Gärtner between 105 and 120; by the Riva-Rocci between 90 and 97.

28th. Second examination several hours after labor, which was easy, though artificially induced. The cardiac dulness extends less far above, but is otherwise unchanged. Below the lower line of

dulness a pulsation is distinctly felt. Apex now found in fourth and fifth interspaces. Outer border is still in the anterior axillary line. Murmurs are unchanged. Blood pressure: Gärtner between 110 and 127; Riva-Rocci between 96 and 97. In this case, also, the mitral regurgitant lesion caused no symptoms during the progress of the labor.

CASE 10. *Cardiac dilatation.*—Olivia E., aged twenty-five years, colored; third pregnancy. First examination April 30, 1902. The patient is rather fat. She states that her former labors were easy. She has had no swelling of the feet or other symptoms, except some shortness of breath on exertion. The abdomen is of usual size; tension normal. Cardiac dulness begins above at the upper border of the second rib, extends on the right to the right border of the sternum. Apex felt in the fifth interspace in the anterior axillary line. At the apex a rather faint systolic murmur covers the first sound, and this murmur is audible over the body of the heart to the left of the sternum. The second sounds are loud. Pulse, 84. Blood pressure: Riva-Rocci, 115 to 120; greatest pulsation occurs at 100. Patient was delivered 10.30 P.M. of April 30, 1902, the labor being uneventful. Examination made twenty hours later showed no change in the cardiac condition. Blood pressure by the Riva-Rocci averaged 132; greatest pulsation averaged 118. Pulse, 76.

May 2*d*. Murmur is indistinct. Apex position unchanged. Blood pressure by Riva-Rocci averaged 130; greatest pulsation 110. Pulse, 76.

4*th*. Blood pressure: Riva-Rocci, 124; greatest pulsation 110. Pulse, 100.

19*th*. The cardiac area remains as large as on former examinations. The apex is in fifth interspace in the anterior axillary line. No murmurs can now be heard. The second pulmonic sound is accentuated. Blood pressure: Riva-Rocci averages 122; greatest pulsation 102. Pulse 76.

CASE 11. *Cardiac dilatation.*—Mrs. B., aged twenty-four years, white; first pregnancy. Examined April 14, 1902. The patient had two chills within the previous twenty-four hours, and at the time of examination she had a temperature of 101°, with a pulse of 136. The abdomen is greatly distended and tympanitic, and the

stomach tympany is especially high, so that no superficial dulness is obtainable. The outer border of heart is made by palpation to be in the anterior axillary line, and the apex apparently in the third interspace; at least in this place the pulsation is most strongly felt. Over the base of the heart is heard a systolic murmur and an accentuation of the pulmonic second sound. Blood pressure averages by the Riva-Rocci 106, and by the Gärtner 108.

15th. Second examination made twelve hours after delivery. The cardiac area is larger than before. Pulsation is visible over most of the area to the left of the sternum as high as the second interspace. The murmur is still audible, but the accentuation of the pulmonic second sound is much less marked. The pulse is 140 and of poor quality and the patient looks very ill. The blood pressure by the Riva-Rocci averages 96; by the Gärtner, 102. This is probably a case of dilatation due to the toxæmia associated with the fever, as no history of previous heart trouble was obtainable.

CONCLUSIONS. The conclusions arrived at by us were that there is not, during pregnancy, any hypertrophy of the left ventricle, nor any special increase in its work. The increase of dulness toward the left is due to the upward displacement of the diaphragm and the consequent displacement of the heart in an upward and outward direction.

The comparative outlines before and after labor show a rapid return to the normal position.

We were struck by the frequency of an increase in the extension of dulness toward the left in the second and third interspaces and by the frequency of distinct pulsation in the same area. In the absence of any evidence of retraction of the lung and in view of the fact that the pulsation discovered in this region was distinctly marked, it is evident that this condition of things is ascribable to distention of the conus arteriosus and root of the pulmonary artery. The frequent presence of a systolic murmur most clearly audible in the same area further substantiates this opinion. Moreover, the position of the right border of the heart seemed on the average somewhat too far toward the right, which, with the conditions present at the root of the pulmonary artery, convinced us that

there is probably during the later months of pregnancy some continuous dilatation of the right ventricle, though this is apparently of very moderate degree. Such a state of affairs can scarcely be regarded as surprising when we reflect that the upward displacement of the diaphragm and pressure upon the lungs must necessarily increase the difficulties of the pulmonary circulation. Our belief in the existence of a dilatation of the right ventricle is, however, based upon observed facts rather than upon theoretical deductions.

The condition of the abdominal recti is important from the point of view of the circulation. In multiparæ separation of the recti materially lessens the tendency to displacement of the diaphragm, and diminishes in a corresponding degree the displacement of the heart during pregnancy. After delivery this diastasis of the recti, however, may occasion a downward displacement of the apex of the heart, and the contrast before and after labor may be quite as pronounced as in primiparæ, though the first position occupied may not have been far from the normal. Later, if the separation of the muscles is not considerable and the normal tone of the abdominal walls is regained a restitution to the normal of the heart and its apex occurs.

The investigations of the blood pressure made by us show conclusively that there is no material increase of this pressure before or after labor. During labor we sometimes found notable increase in the blood pressure, such as has also been observed by others.

When a comparison of the figures is attempted, the difficulties due to the imperfections of apparatus and the personal equation of the observer become apparent. Fellner, using the Gärtner tonometer, found the pressure during pregnancy from 80 mm. to 100 mm. These figures, it will be seen, are materially lower than those frequently observed by us. During labor there was an increase during pains of 10 mm. in the earlier period and later a more decided increase. After labor the pressure fell to a point lower than it had been before. Lebedeff and Porochjakow (*Centralbl. f. Gynäkol.*, January 5, 1884), using the sphygmomanometer of von Basch, found a difference of 18 mm. during the pains of labor. Of course, such increase may be explained by the holding of breath, the expulsive efforts, etc. MacDonald, with Mahomed's

instrument, before labor obtained the best pulse tracings when the pressure was 5.6 ounces, and recorded as an average obliterating pressure 16.9 ounces; after labor the figures were 5 ounces and 16 ounces, respectively; while in healthy non-pregnant women 4 ounces and 13.5 ounces are stated as being normal. These results are in no way substantiated by more recent methods of observation.

In conclusion, we wish to express our thanks to Dr. B. C. Hirst for his kind permission to study the patients under his care in the maternity department of the University Hospital.

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